Menopause and cardiovascular disease

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Abstract
Cardiovascular disease is very common in women. It is still under diagnosed and under treated. Many women are not having their risk factors for cardiovascular disease properly addressed. Many healthcare professionals are uncertain about the role of hormones in cardiovascular disease. This article gives an overview of the most important risk factors for cardiovascular disease and how to manage those risk factors appropriately, based on the available evidence.

Keywords
Estrogen, heart disease, hormone replacement therapy, menopause

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in postmenopausal women.\textsuperscript{1} Cardiovascular disease causes 26\% of all deaths in the UK; an average of 435 people each day. Around 42,000 people under the age of 75 in the UK die from CVD each year.\textsuperscript{2}

Healthcare costs relating to cardiovascular disease are estimated at £9 billion each year. The cost of CVD to the UK economy (including premature death, disability and informal costs) is estimated to be £19 billion each year.\textsuperscript{2}

There are differences between men and women regarding clinical presentation of cardiovascular disease as well as regarding pathophysiology and response to treatment. CVD in women is frequently underdiagnosed. Women often have a lower perception of risk which can result in a delayed diagnosis and failure to recognise their symptoms. Women are more likely to have stable plaques and a greater occurrence of microvascular lesions compared to men.\textsuperscript{3}

Cardiovascular disease and menopause
The risk of CVD greatly increases after the menopause when estrogen levels reduce. Typically, women are around 10 years older than men at first presentation of atherosclerotic coronary heart disease and this can be related to decline in ovarian hormone concentrations during the menopausal transition and beyond.\textsuperscript{4} Estrogens and also testosterone are involved in the development of CVD in women, and these hormones have a role in endothelial function, vascular tone and also in cardiac function.\textsuperscript{5}

Risk factors

Hypertension
Hypertension is a very important risk factor for heart disease in women and it is generally under-diagnosed and under-treated. In developed countries, 30\% of adult women have hypertension, and this prevalence is even higher in low–middle-income countries, reaching up to 53\%.\textsuperscript{6,7}

For every 20mmHg systolic and 10mmHg diastolic blood pressure increase, there is a doubling of mortality both from coronary heart disease and stroke for women aged 40–89 years.\textsuperscript{8} Although younger women are at lower absolute cardiovascular risk than older women, this should not impede the detection and effective management of hypertension at any age.

The prevalence of hypertension in postmenopausal women is more than twice the prevalence in premenopausal women.\textsuperscript{9} Even moderate or borderline hypertension (<140/90 mmHg) causes more endothelial dysfunction and cardiovascular complications in women than in men.\textsuperscript{10}

Cholesterol
The incidence of raised total cholesterol concentration >6.5 mmol/L is equivalent or greater in women
compared to men aged 50 years and older in the UK.\textsuperscript{11} Raised cholesterol is a risk factor for CVD.

**Early menopause**

The average age of the menopause is approximately 51 years. Women with premature menopause (aged < 40 years), either natural or surgical, have an increased risk of CVD risk.\textsuperscript{12–15}

**Menopause**

Low estrogen levels can be associated with a greater future risk of heart disease and osteoporosis, and it is important that women know that there are beneficial health effects of taking estrogen in addition to hormone replacement therapy (HRT) improving their symptoms.\textsuperscript{16–18} Estrogens can modulate vascular function by targeting estrogen receptors in endothelial cells and also in vascular smooth muscle cells. Estrogens can also lead to the release of nitric oxide and prostacyclin, which are both vasodilators. In addition, they can lead to a reduction in the production of endothelin and angiotensin II which are vasoconstrictors.

Ageing and atherosclerosis can lead to damage of the vascular wall with loss of estrogen receptors. In addition, a reduction in circulating estrogen leads to a reduction in estrogen receptors in both the vascular endothelium and also the vascular smooth cells. Estrogens also reduce inflammation and can reduce the secretion of pro-atherogenic cytokines such as tumour necrosis factor alpha (TNF-\(\alpha\)) and can increase prostaglandin I\(_2\), which reduces oxidative stress and also platelet activation.

There is evidence that women of any age with vasomotor symptoms have a worse cardiovascular risk profile (increased risk of CVD, CHD, or ischaemic stroke) compared with women without vasomotor symptoms. Women experiencing vasomotor symptom have significantly higher systolic and diastolic blood pressures, higher circulating total cholesterol levels and a higher body mass index than their counterparts with no symptoms.\textsuperscript{19,20}

**Management of CVD risk factors in women**

**Hypertension**

Current guidelines are available regarding managing hypertension in women and it is important that these are followed.\textsuperscript{21,22} However, the rate of hypertensive women detected, treated and subsequently well controlled is estimated to be only 10%.\textsuperscript{23}

**Cholesterol**

Current guidelines on the management of dyslipidemias recommend considering statin use for primary prevention in women who have an elevated CVD risk.\textsuperscript{24,25} In addition, they should be prescribed to women for secondary prevention of cardiovascular events; the recommendations and targets are the same for women as for men.

HRT can improve lipid profiles and lead to a reduction in low-density lipoprotein cholesterol.\textsuperscript{26} In addition, HRT can produce significant increases in high-density lipoprotein cholesterol and decreases in lipoprotein(a) compared to statins which actually have little effect on these levels.\textsuperscript{27}

**Early menopause**

In women with premature surgical menopause, estrogen treatment has been shown to be associated with significant protection against ischaemic heart disease.\textsuperscript{28} The benefit from estrogen has been shown to be the most pronounced for current users and for women who started treatment within 1 year after their surgery. All women with premature ovarian insufficiency (POI) should receive hormone therapy at least until the age of the natural menopause (51 years) unless there are contraindications.\textsuperscript{17,18,29,30}

**Menopause and HRT**

The benefits and risks of HRT vary by dosage, route of administration and timing of initiation.\textsuperscript{31} Estrogen in HRT can have a protective effective in early atherogenesis compared to a potentially harmful effect in established atherosclerosis.\textsuperscript{32} In early atherogenesis, estrogen has beneficial effects by improving plasma lipids, maintaining endothelial cell integrity and promoting nitric oxide production. Conversely, in established atherosclerosis, estrogen can increase matrix metalloproteinase (MMP) expression which can lead to instability of the fibrous cap and rupture of the atheromatous plaque (Figure 1).

HRT with estrogens in older postmenopausal women has not shown to be associated with a reduction in CVD events.\textsuperscript{16,33} However, data accumulated from numerous studies have shown that, in women under the age of 60 years with symptoms or other indications, initiating HRT near their menopause provides a favourable benefit:risk ratio. This is reflected in current National Institute for Health and Care Excellence (NICE) and International Menopause Society guideline recommendations.\textsuperscript{17,18} This means that the cardioprotective effect of estrogen replacement therapy is seen in postmenopausal women in a time-dependent manner.
Studies have shown that there is a lower incidence of CVD in women taking HRT within 10 years of their menopause. A Cochrane meta-analysis showed that for women taking HRT within 10 years of their menopause, there is a 0.70 relative risk reduction of all-cause mortality and a 0.52 relative risk reduction of coronary heart disease mortality. The CVD benefit of taking HRT is greatest the earlier a woman starts HRT with respect to her perimenopause or menopause. A Finnish study has shown that using any HRT for at least 10 years is associated with 19 fewer CHD deaths and 7 fewer stroke deaths per 1000 women. This concept is often referred to as the ‘timing hypothesis’ as the cardiovascular effects of HRT strongly depend on individual vascular health and the time since their menopause before starting HRT.

The Danish Osteoporosis Prevention Study was undertaken to investigate the long-term effect of HRT on cardiovascular outcomes in recently postmenopausal women. This study found that after 10 years of randomised treatments, women receiving HRT which

Figure 1. Differential protective effects of estrogens in hormone replacement therapy in early atherogenesis and harmful effects in established atherosclerosis. Differential protective effects of estrogenic HRT in early atherogenesis and harmful effects in established atherosclerosis. In early atherogenesis, cardiovascular risk factors, haemodynamic forces and circulating inflammatory factors cause endothelial cell injury resulting in decreased NO production and increased EC permeability. Once injured, the endothelium increases the expression of leukocyte adhesion molecules, which increases the adherence of macrophages and other leukocytes. The increased EC permeability allows entry of leukocytes and lipoproteins into the subendothelial space. Oxidized lipoproteins are taken up by macrophages and SMCs to form foam cells (fatty streak). E2 has beneficial effects on early atherosclerotic lesions by changing the plasma lipid profile, maintaining EC integrity and promoting NO production. In established atherosclerosis foam cells at the central-most position of the developing atheroma become necrotic and form the central lipid core, whereas the shoulder regions contain SMCs, macrophages and other leukocytes. Platelet-derived growth factor and transforming growth factor-β stimulates SMC migration and collagen formation in the subendothelial space, as well as formation of the fibrous cap. E2 increases MMP expression in established atherosclerosis, causing instability of the fibrous cap and rupture of the plaque.

CAM: cell adhesion molecule; EC: endothelial cell; ET-1: endothelin-1; LDL: low density lipoprotein; MCP-1: monocyte chemotactic protein-1; MMP: matrix metalloproteinase; NO: nitric oxide; PGI2: prostacyclin; TNF-α: tumour necrosis factor-α; VSMC: vascular smooth muscle cell.

started early after the menopause had a significant reduction in risk of cardiovascular mortality, heart failure or myocardial infarction.

In the Early versus Late Intervention Trial with Estradiol, postmenopausal women free from cardiovascular disease were stratified according to time since menopause and were randomly assigned to receive either 17β-estradiol plus micronised progesterone vaginal gel or placebo over a median of 5 years. Compared with placebo, estrogen treatment resulted in a significantly slower progression of coronary artery intima media thickness among women who initiated HRT less than 6 years after menopause.

NICE state that women should be informed that the presence of cardiovascular risk factors is not a contra-indication to HRT and also that it is essential to optimally manage any underlying cardiovascular risk factors (e.g. hypertension, high cholesterol). This means that having raised blood pressure is not a contra-indication to taking HRT nor a reason to stop prescribing HRT. Elevated blood pressure should be addressed and promptly managed in women as it should be for women who are not taking HRT.

Avoiding HRT in menopausal women can actually be detrimental to their future health in terms of cardiovascular disease and also osteoporosis. Some experts are now recommending that HRT should now be considered as part of a general prevention strategy for women at the onset of the menopause.

There is some evidence that cardiovascular morbidity and mortality can increase in the first year after HRT is stopped, although it is unclear whether tapering the dose reduces this risk. This risk was actually greater in women who were under 60 years at the initiation or discontinuation of HRT use.

The MMPs and their tissue inhibitors are important for vascular remodelling. Estradiol can increase the release of MMPs in a dose-dependent manner. Low-dose estrogen may lead to increases in MMPs which can normalise vascular remodelling, whereas high doses of estrogen may produce large increases in MMPs and lead excessive remodelling. This means that the starting dose of estrogen in women with established atheroma should be as low as possible to improve symptoms. Low doses of estrogen are unlikely to be harmful in this respect.

Progestogens have differing effects on cardiovascular risk. In general, those progestogens more like progesterone have been associated with a lower effect on cardiovascular disease compared to the more androgenic progestogens. Micronised progesterone seems to have a neutral or beneficial effect on blood pressure in post-menopausal women. In contrast to other progestogens, progesterone has been shown to antagonise the effect of aldosterone, causing natriuresis and also a reduction in blood pressure.

**Summary**

Prevention of cardiovascular disease in women, as for men, should be started early. Consultations with perimenopausal and menopausal woman are perfect opportunities to assess cardiovascular risk. More women should ideally be considered for HRT at an earlier stage in order to gain maximum cardiovascular protection. Women with POI, early menopause and women within 10 years of their menopause can potentially gain significant improvements in their cardiovascular health, as well as their general health, by being offered HRT. The education of healthcare professionals is paramount when reflecting on the potential health benefits to be gained by taking HRT.

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