Risk factors for cardiovascular disease in women: assessment and management

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Coronary heart disease (CHD) is the most important cause of death and disability among older women. A 50-year-old woman has a 46% risk of having CHD and a 31% risk of dying from it. Female CHD patients have a distinct clinical presentation, which includes more severe thromboembolic disease without coronary arteriosclerosis. Syndrome X also appears to be more prevalent in women. Oestrogen deficiency may be a trigger for this syndrome. The magnitude of the effect of various risk factors may also differ between women and men. In addition, there are risk factors unique to women. Lipid profiles differ between men and women. After menopause, the lipid profile changes unfavourably, with increasing levels of LDL cholesterol and decreasing levels of HDL cholesterol. Cigarette smoking, hypertension, diabetes mellitus, and obesity are all recognised risk factors for CHD in women.

It is important to recognise that risk factors for CHD differ between men and women. Advising women to quit cigarette smoking, avoid obesity, increase physical activity, and prevent and treat hypertension and hyperlipidaemia will result in a reduction in CHD risk. Additional studies are needed to further contribute to our understanding of the complex risk factors underlying the development of CHD in women.

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Introduction

Coronary heart disease (CHD) is the leading cause of death and disability among older women. In Sweden it is the main cause of death for women over the age of 55 years and for men over the age of 45 years, and in the United States it is the primary cause of death among women over the age of 60 years. In this age group, one in four women, as well as one in four men, die of CHD. The rates of mortality from CHD have been falling since the 1960s, but in the United States the rate of decline has been slower among women than among men since 1979. In Sweden, the decline in the mortality rate for women is also slower than for men, although the change came later. The decline in mortality rates for women was reduced by 20% and for men by 30%, leading to a reduction in gender differences in mortality from myocardial infarction (MI).

France has the lowest mortality from MI in Europe (21/100 000), and other Mediterranean countries also have low mortality rates. The United Kingdom, Ireland, Hungary, Poland, Russia, and other eastern European countries have the highest incidence of death from cardiovascular diseases in Europe. A 50-year-old woman has a 46% risk of having CHD during the rest of her life and a 31% risk of dying of CHD. In comparison, her chances of having or dying of breast cancer are 10% and 3% respectively, and her chances of having or dying of a hip fracture are 15% and 1.5% respectively.

Clinical presentation and assessment

The Framingham Study reported that more women than men have angina pectoris as their initial symptom of CHD (65% vs 35%), while fewer women than men (29% vs 43%) suffer an MI as their first manifestation. The Framingham Study reported that women are more likely than men to experience an unrecognized, or silent MI, which would later be diagnosed during a routine examination. The Framingham Study reported that women are more likely than men to experience an unrecognized, or silent MI, which would later be diagnosed during a routine examination. Women may also delay seeking medical attention if they suspect an MI. MI is more often fatal in women than in men, and, in fact, 36% of women who die of coronary artery disease present with sudden cardiac death or MI. Interestingly, women with recurrent silent MI have an increased overall mortality. Women are usually seven to ten years older than men at the time they experience an MI, so the symptoms may result from age rather than gender. MI occurs with more seasonal variation in women than in men.
men, with an increase in incidence in the autumn and winter.

Women presenting with an acute infarction have the same weekly number of episodes, precipitants of angina, and frequency of angina at rest as do men. Presenting symptoms in both men and women include chest pain with typical radiation, nausea, and diaphoresis, but men are more likely than women to present initially with ventricular tachycardia.

Electrocardiographic changes detected with vector analysis during the first 24 h after MI differ between men and women. Women have fewer ST-elevations during an acute MI, which might explain why women experience less thrombolysis in connection with MI than men. The same is seen during PTCA (percutaneous transluminal coronary angioplasty). Women probably have less advanced coronary stenosis than men at the time of infarction, and it is postulated, but not really proven, that women have more non-Q infarctions. Mechanical complications associated with MI occur more in women, possibly because women have less collateral vessel development, and tend to be older and have more advanced disease than men.

Women are less likely than men to be referred for coronary angiography, but the results of angiograms are interesting. After MI, women more often have normal findings in coronary angiograms than do men, and also have less collateral vessel development. More than 50% of women with angina pectoris undergoing coronary angiography have normal arteries, compared with 16% of men.

A review of the angiographic findings in almost 5000 patients showed that women with atypical angina pectoris seldom have coronary artery disease. According to this report, a 45-year-old woman with atypical angina pectoris has a 13% chance of having CHD. These calculations are based only on sex and age; however, and if other risk factors are considered, like hypertension, hyperlipidaemia, diabetes mellitus, and resting electrocardiogram with ST-T wave changes, the likelihood of coronary artery disease occurring would be higher. The fact that prior epidemiological studies have not considered other risk factors, like smoking, obesity, and physical activity, makes it difficult to estimate the likelihood of CHD in women.

Coronary angiography may not be the best method for diagnosing coronary artery disease. New techniques like intravascular ultrasound and magnetic resonance imaging detect atheromatosis in spite of apparently normal coronary angiography results. Syndrome X, which is angina pectoris and positive exercise-related ECG changes in the presence of normal coronary angiograms, appears to be more prevalent in women than in men. It is related to menopause, with an overall imbalance in vasomotor tone in all vessels including the coronaries, and oestrogen deficiency may be a trigger.

Non-invasive diagnostic testing of coronary artery disease in women has less predictive value than it does in men. A study performed in 1975 reported an incidence of true-positive exercise tests of 89% in men and 33% in women, using positive coronary angiograms as a comparison. False-positive results were 8% for men and 67% for women. Thus, a positive exercise test is of little value in predicting the presence of significant coronary artery disease in women. This result was confirmed in several later studies, including one from our own group. Rate-pressure product and exercise capacity may be the best diagnostic parameters in women. Stress radionuclide ventriculography performed in women with coronary artery disease appears to demonstrate left ventricular dysfunction during exercise, but the poor specificity of the exercise ejection fraction in females may limit the diagnostic applicability of this test. Stress ECG combined with technetium scintigraphy provides both the sensitivity and specificity required for diagnosis in women. Scan interpretation may be complicated because breast tissue attenuates myocardial activity, resulting in defects in the anterior and septal distributions. The shifting of breast tissue may lead one to conclude that redistribution has occurred. Gender-matched normal databases should be constructed for quantitative scan analysis.

**Risk factors**

The magnitude of the effects of various risk factors for coronary heart disease may be different in men and women, and there are risk factors that are unique to women. Conclusions drawn from studies performed only on men cannot, therefore, be extrapolated to women.

**Lipoproteins**

Most lipid-lowering trials have involved only men. Because the lipid profile differs between men and women and the life patterns of lipoprotein levels are different, it is difficult to determine if the results of these trials pertain to women.

Before menopause, low-density lipoprotein (LDL) cholesterol levels are lower in women than in men. After menopause, the LDL cholesterol levels increase to levels greater than those in men. Triglyceride levels and a lipoprotein a particle (LPa) also increase, and high-density lipoprotein (HDL) cholesterol levels decrease after menopause. HDL cholesterol levels are higher in women than in men, however, over the entire life span. The increase in LDL cholesterol levels after menopause might be caused by decreased LDL receptor activity. The enzyme hepatic lipase decreases also, with decreasing oestrogen levels, which might be important for HDL cholesterol concentrations. The increase in LDL cholesterol levels after menopause might be caused by decreased LDL receptor activity.

A direct antioxidant effect on LDL cholesterol has also been reported with 17 β-oestradiol. Oestrogen for post-menopausal women may act in a manner similar to the statins, a new class of lipid-lowering drugs.
Primary prevention and lipoproteins in women

The results of epidemiological studies suggest that elevated total cholesterol and triglycerides predict CHD among middle-aged and older women. High triglyceride levels (often associated with lifestyle factors like obesity, stress, and alcohol intake) are even better predictors for CHD in women, and are often related to the HDL cholesterol fraction. LDL cholesterol levels appear to be less important in diagnosing CHD in younger women, but for older women as well as for men, LDL levels are a powerful predictor of MI. As well as age, another important factor in evaluating the risk associated with an elevated LDL concentration is the number of years since menopause.

Data on primary prevention of CHD by modification of the lipid profile in healthy women are limited. It is still unclear whether healthy women with modestly raised cholesterol levels benefit from lipid-lowering interventions. If such an intervention is undertaken, the aim should be to raise HDL cholesterol levels and lower LDL cholesterol levels, similar to how oestrogens function. In the U.S.A. the Women's Health Initiative (WHI) is studying 60,000 women to evaluate, among other things, the effect of lipid-lowering interventions on healthy women.

Secondary prevention and lipoproteins in women

Few secondary prevention intervention trials have included women at all, or in large enough numbers to provide significant information. In one trial including over 7000 women, however, lovastatin was tested and no gender difference was found in its effects on LDL cholesterol, triglyceride, or HDL cholesterol levels. The only trial that had hard end-points like mortality, reinfarction, and cardiovascular events in a lipid-lowering trial was the 4 S study. This study included about 700 women who had had MI or angina pectoris; this number was too small to show a reduction in total mortality. A clear reduction was found in reinfarction and coronary artery disease events in women.

The results of these studies suggest that women with hypercholesterolaemia after a MI should change their eating habits and be treated with lipid-lowering drugs to lower their cholesterol levels. A low-fat/cholesterol diet alone may be more beneficial for men than for women, however.

Cigarette smoking

Smoking is more common among younger women than younger men in most western countries, and it is an increasing health problem. Adult women have not quit smoking at the same rate as men, probably because they fear gaining weight. The number of women who start to smoke in their teenage years and continue to smoke throughout adult life is, therefore, increasing. At the present time, peri-menopausal women form the first cohort of women ever with a lifetime history of cigarette smoking comparable with the male cohorts. Cigarette smoking alters the oestrogen metabolism in pre- and post-menopausal women. The resulting lower oestrogen levels cause a premature menopause, which increases the risks of CHD. Increased coronary heart disease and adverse lipid profiles have been demonstrated in middle-aged women who smoke cigarettes. Women who are heavy smokers (>20 cigarettes daily) have a much greater risk of CHD than do women who do not smoke. Even female ‘light smokers’ (1-4 cigarettes daily) have more than twice the risk of coronary artery disease than non-smokers. Passive smoking and smoking ‘low-yield’ cigarettes (reduced tar, nicotine, and carbon monoxide) are also dangerous for women. Among healthy women, the progression of aortic calcification correlates with the number of cigarettes smoked daily. Quitting smoking after many years will reduce, but not eliminate, the risk of aortic calcification.

Because of the high prevalence of smoking among women, reducing cigarette smoking will probably be the single most effective measure to prevent CHD on a population basis.

Hypertension

Until about 20 years ago it was generally accepted that women, especially older women, tolerate higher blood pressure and that hypertension in this group should not be treated. More recently, however, several studies have shown a strong association between elevated blood pressure and CHD in women. Isolated systolic hypertension is more prevalent among older women with loss of arterial elasticity (approximately 30% of women over 65 years), and these women have an elevated risk of death from stroke or coronary heart disease.

Early menopause is associated with an increase in diastolic blood pressure. Oestrogen therapy generally reduces the blood pressure of post-menopausal women, particularly for women whose initial blood pressure is slightly elevated. It has been debated whether or not to treat mild-to-moderate hypertension (i.e. diastolic BP between 90 and 114 mmHg). A meta-analysis of randomized drug treatment trials evaluated therapy for mild-to-moderate hypertension. These trials involved 37,000 subjects, 47% of whom were women. The meta-analysis showed that a mean decrease of 6 mmHg in diastolic pressure significantly reduced overall mortality from vascular disease by 21%, stroke by 42%, and coronary heart disease by 14%. Hypertension studies conducted in Europe and the United States involving over 13,000 women reported a decrease in all causes of mortality among treated vs control women, but these trials...
were not designed to examine mortality in women specifically[47,48].

Three large hypertension trials including a large number of women have shown the benefits of therapy, with even better results of blood pressure lowering in older women than in men. The results of these trials showed significant reduction in death from stroke and coronary-related events in patients up to 84 years of age with either mixed or isolated systolic hypertension[52-54].

In the Nordic countries, hypertensive women receive diuretics, especially thiazide diuretics, much more than do hypertensive men. In spite of being the cheapest hypertensive drug, it might be unsuitable for women because it increases cholesterol levels, and LDL cholesterol levels rise markedly with age in post-menopausal women.

In conclusion, we very little about the interactions between hormone replacement therapy and different antihypertensive agents. Oestrogens may act like calcium channel blockers, suggesting that a possible synergistic effect with other hypertensive drugs may be possible.

**Diabetes mellitus**

The incidence of diabetes mellitus in women increases manyfold after menopause. The disease process in diabetes may impair oestrogen binding and counteract the protection against CHD that endogenous oestrogen confers on premenopausal women. Diabetes may also exacerbate the effects of known coronary risk factors in women. Diabetic women have a higher mortality and morbidity rate from CHD than diabetic men[52-54], which suggests that sex hormones influence glucose and insulin metabolism.

Impaired glucose tolerance is predictive of CHD, and the increased risk is likely to be mediated through insulin resistance and hyperinsulinaemia. Insulin resistance induces adverse changes in lipids and lipoproteins and may be of special importance in female patients with syndrome X (typical angina pectoris, pathological exercise test, and angiographically smooth coronary arteries on the coronary angiogram). Oestrogens may affect glucose tolerance in a positive way and be important for female patients with syndrome X.

Three percent of pregnant women develop gestational diabetes, and this may be a marker for increased risk of CHD. About one-third of these women will later develop non-insulin dependent diabetes mellitus, and also hypertension, adverse lipid profiles, and abnormal electrocardiograms.

**Obesity and body fat distribution**

Obesity increases the risk of coronary heart disease. A woman with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 29 or higher has three times the risk that a lean woman has[55]. A large part of the increase in risk is attributable to the influence of adiposity on blood pressure, glucose tolerance, and lipid levels. After adjustment for these variables, a moderate residual effect persists. Women who maintain an ideal body weight have a 35—60% lower risk of MI than women who become obese, according to the Framingham Study data[56].

In women, there are interrelationships among body fat, oestrogen synthesis, and lipoprotein metabolism. Obese women have higher oestrone levels in adipose tissue. Oestrone is less active compared to oestradiol, but it still plays a role. Obese women reach menopause later than lean women, which provides greater protection against osteoporosis, but also promotes an increased risk of developing endometrial cancer. These trends indicate that obese and lean women have different oestrone activities. It is still unclear what obesity and oestrone levels will mean for the risk of CHD.

The type of obesity (android, abdominal, or central) is an independent risk for cardiovascular disease in women and also independent of the degree of overall obesity. The risk for CHD rises among women with a waist-to-hip ratio higher than 0.8. These women generally have insulin resistance, reduced HDL cholesterol levels, hypertriglyceridaemia, hypertension, and decreased sex hormone-binding globulin levels. This characteristic is sometimes combined with the cardiological syndrome X[57,58].

Higher levels of free testosterone have been found in healthy women with central adiposity compared with women with greater peripheral adiposity[59]. Females with abdominal central fat have elevated plasminogen-activator-inhibitor-1 antigen and reduced fibrinolytic potential[60], and tend to smoke cigarettes and have a more sedentary lifestyle than lean women.

**Haemostasis**

The majority of the studies investigating the effects of aspirin on primary prevention were performed on men, while the evidence for aspirin's effects on women comes mainly from observational data. Randomized clinical trials of aspirin use in healthy women are, however, underway.

The results of the Nurses' Health Study showed that the incidence of first MI was reduced in women taking low-dose aspirin and aged 50 years or more, compared with women reporting no aspirin use. No protective effect for stroke was seen[61]. Smaller experimental studies[62] suggest a sex difference in the antithrombotic effects of aspirin.

Thrombolytic treatment in acute MI seems to have the same beneficial effects in both women and men. Women with MI seemed to have good acute effects from streptokinase treatment, but the relative reduction in mortality in the follow-up was less than that of men in three big studies[63-65]. Women also appeared to derive less benefit from streptokinase, aspirin, or their
combination when compared to men in the ISIS-2 study\cite{10}. Female patients receiving tPA within 4 h had greater frequency of death and combined reinfarction and death in the TIMI study\cite{11}. Women with CHD had higher plasma levels of von Willebrand factor antigen, PAI-1, and fibrinogen than women in a matched control group in the Stockholm Study\cite{12}. Fibrinogen and LP(a) have been linked to CHD in women\cite{13}. The role of post-menopausal hormonal replacement therapy and venous thrombosis and stroke is still unclear, but there is, so far, no hard evidence of an oestrogen-induced increased risk.

\section*{Physical activity}

There is little direct evidence that physical activity reduces the incidence of coronary heart disease in women. Moderate levels of exercise appear to result in reduced weight, blood pressure, and cholesterol levels. The influence of physical activity on lipid levels in women differs in pre- vs post-menopausal women. In post-menopausal women, exercise decreases endogenous oestrogen concentrations via a reduction in body fat, and this may lead to unfavourable levels of HDL cholesterol and LDL cholesterol. Higher endogenous levels of oestrone are linked to higher HDL cholesterol and lower LDL cholesterol levels among pre- and post-menopausal women\cite{14}.

\section*{Psychosocial risk factors}

Psychosocial risk factors differ between men and women, as shown by Frankenhauser et al.\cite{15} who studied middle managers at the Swedish Volvo company. They found that the female managers arriving home from work had a rise in noradrenaline levels in urine and an increase in pulse and blood pressure, compared with male managers.

So far, few studies have included an adequate number of women to be able to make conclusions concerning psychosocial risk factors for CHD. The Stockholm Study on psychosocial risk factors in women with CHD found that patients were more depressed, had more signs of vital exhaustion, less ability to cope, worse quality of life, and worse belief in the future as compared with matched controls. Type A behaviour and social support were not important, but low education and high work stress were important risk factors for CHD\cite{16}.

\section*{The role of hormones}

One reason why women suffer from CHD 10-15 years later than men relates to hormone differences. Indirect evidence for this hypothesis is that premature menopause and premature oophorectomy consistently increase the risk for MI in women\cite{17}. Most epidemiological studies have shown an independent, statistically significant increased rate of CHD among women with more and/or earlier reproductive events\cite{18}. The decreasing levels of oestrogens with age and the concomitant increased LDL cholesterol level are natural, unique risk factors for female patients. The ten-year gap in development of cardiovascular disease between older men and older women is also due to a decelerated increase in the rate of mortality for coronary heart disease and to earlier mortality among men. Postmenopausal oestrogen replacement apparently protects against CHD in women, partly through its beneficial effects on lipid levels and on vasculature and endothelial function.

\section*{Management}

It is important to recognize that risk factors for coronary heart disease in women differ from those in men. It is clear that advising women to quit cigarette smoking, avoid obesity, and increase physical activity, as well as to prevent and treat hypertension and hyperlipidaemia, will result in a reduction in the risk of coronary disease. Stress management will probably be of great importance for women also, but more studies need to be performed in this area.

\section*{References}


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