

CARDIOVASCULAR RISK FACTORS IN WOMEN

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INTRODUCTION

Ischaemic heart disease (IHD) remains the leading killer of both men and women in developed nations. World Health Organisation data reveal that in Europe 55% of female deaths and 43% of male deaths are attributable to cardiovascular disease (CVD).¹

The notion that IHD is a male disease has led to the underestimation of disease burden in women. When age-adjusted data are considered, cardiovascular disease is more common in males. However, the prevalence of heart disease in the population >65 years is roughly equivalent between the sexes, owing to the higher proportion of women in this group. More women than men have died annually from IHD since 1984.

Heightened physician and patient awareness of the risk factors contributing to CVD and their control with primary and secondary prevention strategies has led to a reduction in disease prevalence and mortality. The magnitude of this regression is smaller in women. Overall, the burden of disease remains high and could be further reduced by recognition and aggressive management of those at risk.

The evaluation and treatment of IHD in women represents a unique and demanding challenge for clinicians. An understanding of gender-related differences in the clinical manifestations, pathophysiology and treatment of IHD is essential to reduce disease prevalence and adverse outcomes. This review will focus on the identification and treatment of cardiovascular risk factors in women.

PLASMA LIPIDS

In blood plasma, lipids such as cholesterol and triglycerides bind to protein molecules to form lipoproteins. These lipid-rich molecules may give rise to atherosclerotic plaque formation. The atherosclerotic potential of each lipoprotein depends on their physical size and concentration in the plasma.

Low-density lipoprotein (LDL) carries most of the cholesterol in blood plasma. There is a strong positive correlation between total and LDL cholesterol levels and cardiovascular risk.² This relationship holds true for patients with and without established CVD and in both males and females. The fundamental role of LDL

in the development of atherosclerosis and consequently the requirement to reduce levels cannot be overstated. Current guidelines recommend reducing LDL cholesterol levels to <3mmol/l in high-risk patients.

Women tend to have less atherogenic lipoprotein subclass profiles than men. Elevated triglyceride levels are more common in women. Hypertriglyceridaemia is associated with the development of atherosclerotic disease but the extent of this correlation is not clearly defined. It is a more potent independent risk factor in women.³ A triglyceride value of >1.7mmol/l is considered to be a marker of increased risk although concentrations of <1.7mmol/l are not deemed a goal of therapy.

Large-scale clinical trials have consistently demonstrated the efficacy of HMG Co-A reductase inhibitors (statins) in reducing LDL and triglyceride levels and subsequent cardiovascular risk.⁴ A large proportion of high-risk women are not treated aggressively enough to reach evidence-based lipid goals.⁵

FEMALE SEX HORMONES

The low incidence of CVD in pre-menopausal women with normal ovulation compared with age-matched men is believed to derive from endogenous sex hormones. Animal studies have consistently demonstrated the anti-atherosclerotic effects of oestrogen.⁶ During the menopause, a woman's oestrogen levels drop to approximately one-tenth that of her pre-menopausal years.⁷ The loss of ovarian hormones has a widespread adverse impact on many cardiovascular risk factors.

Hormone replacement therapy (HRT) comprises oestrogen with or without a progestin. It is used for relief of menopausal symptoms and the prevention of post-menopausal osteoporosis. Observational studies have suggested that women taking HRT have better CVD risk factor profiles and a reduced incidence of coronary artery disease.⁸ However, recent large clinical trials of HRT have not demonstrated a reduction in cardiovascular risk.⁹ Further research into the anti-atherosclerotic effects of HRT is warranted as alternative hormone and dosing regimens still offer the potential to reduce total cardiovascular risk. Currently, the use of hormone replacement solely for

cardioprotection is not recommended.

HYPERTENSION

Hypertension represents an increasingly important medical and public health issue. Its prevalence rises with age, with >50% of people aged 60-69 years and >75% aged above 70 years affected.¹⁰ Observational studies involving over one million people have indicated that death from both IHD and stroke rises progressively and linearly from blood pressure (BP) levels as low as 115mmHg systolic and 75mmHg diastolic upwards.¹¹ For every 20mmHg systolic or 10mmHg diastolic increase in BP there is a doubling of CVD mortality.

The goal of anti-hypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Treating systolic BP and diastolic BP to targets that are <140/90mmHg is associated with a decrease in CVD complications.¹² In patients with hypertension and either diabetes or renal disease, the BP target is <130/80mmHg.^{13,14}

Hypertension is less common in females than in males until the fifth decade of life, when the incidence of hypertension increases in females. The prevalence of hypertension in women is equal to or exceeds that in men during the sixth decade of life.

The oral contraceptive pill (OCP) may cause a small increase in BP but the absolute risk is small.¹⁵ BP levels return to baseline within three months of OCP discontinuation.

The effect of the menopause on BP is controversial. A menopause-related rise in BP has been attributed to a variety of factors, including oestrogen withdrawal, overproduction of pituitary hormones and weight gain. Longitudinal studies have not documented a rise in BP with menopause, while cross-sectional studies have found significantly higher BP in post-menopausal versus pre-menopausal women.¹⁶

There is ongoing debate about the effect of HRT on BP. The Women's Health Initiative (WHI) found an average 1mmHg increase in systolic BP in 8,000 patients randomised to receive conjugated equine oestrogen and medroxyprogesterone acetate as compared with a placebo group.¹⁷ In a cross-sectional analysis of 100,000 women in the WHI cohort, aged 50-79 years, current HRT use was associated with a 25% greater likelihood of hypertension compared with past use or no prior use.¹⁸

Current evidence indicates that the sex of the patient should not influence the decision to treat hypertension to pre-defined treatment goals. The response to anti-hypertensive medications is similar among the sexes. Caution must be exercised when using angiotensin converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age as both are teratogenic.

GLUCOSE

Hyperglycaemia is associated with an elevated risk of developing IHD and other atherosclerotic diseases.^{19,20} Patients with type 1 diabetes have a two- to three-fold increased risk of developing CVD. This is almost exclusively confined to those who have developed diabetic nephropathy.²¹ All patients with type 2 diabetes, regardless of renal status, are at increased risk of CVD.

The prevalence of diabetes is increasing in both men and women. Studies have reported a significantly higher cardiovascular mortality for diabetic women compared to diabetic men.²² The age-adjusted risk of developing CVD doubles in diabetic versus non-diabetic women. Thus, it seems that diabetes negates the 'female advantage' which confers lower IHD prevalence on the majority of women.

SMOKING

Smoking-related death accounts for half of all deaths in long-term tobacco smokers. Over 50% of these deaths are due to CVD.²³ The CVD risk is related to the number of cigarettes smoked daily and the duration of exposure. Cigarette smoking is more prevalent in women. Globally, the number of cigarette smokers is falling; however, the magnitude of decline is less dramatic in women. While the adverse effects of smoking are present in both men and women, they are believed to be slightly more pronounced in women, further reducing their innate protection from CVD.²⁴



OBESITY

Population studies have demonstrated a consistent link between being overweight and total mortality. CVD accounts for the excess mortality among obese subjects.²⁵

Metabolic risk factors tend to cluster in obese patients: insulin resistance, glucose intolerance, low high-density lipoprotein (HDL), small LDL particles, high triglycerides and hypertension. The metabolic syndrome is a clustering of these risk factors and is

more prevalent in women than in men with CVD.^{26,27} The four-year relative risk of cardiac events is doubled for women with the metabolic syndrome compared to those with a normal metabolic profile.²⁸



GENDER DIFFERENCES IN RESPONSE TO THERAPY

Evidence-based pharmacotherapy is essential to reduce morbidity and mortality associated with CVD. Emerging data concerning gender-related differences in the pathogenesis and response to treatment of CVD demonstrate a need for the individualisation of management strategies. Female representation in studies on IHD has risen since the 1980s; however, primary and secondary preventative regimens are largely based on evidence derived from principally male cohorts.

Gender-specific physiological differences exist, including lower body mass index and smaller organ size in women compared with men, resulting in larger distribution volumes in males. Women have a larger proportion of body fat, which may increase the distribution volume for lipophilic drugs. Pharmacokinetic studies have demonstrated differences in the activity of drug-metabolising enzymes between the sexes. The enzymes of the cytochrome P450 system, which is responsible for the metabolism of many cardiovascular drugs, may account for gender-specific response to treatment.

The Physician's Health Study showed that aspirin significantly reduced the risk of myocardial infarction but not stroke or cardiovascular mortality in men.²⁹ In the Women's Health Study, aspirin did not reduce the risk of myocardial infarction or cardiovascular mortality in women. A significant reduction in the risk of stroke was observed however.³⁰ The contrasting response to long-term aspirin prescription demonstrates the need for gender-specific prescription.

CONCLUSION

CVD kills more women than all other disease entities combined; it is underdiagnosed and undertreated resulting in significantly poorer outcomes in women.

Improved understanding of gender-related differences in risk factor profiles and treatment will further reduce cardiovascular morbidity and mortality in women.

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