

Underestimating risk in women delays diagnosis of CVD

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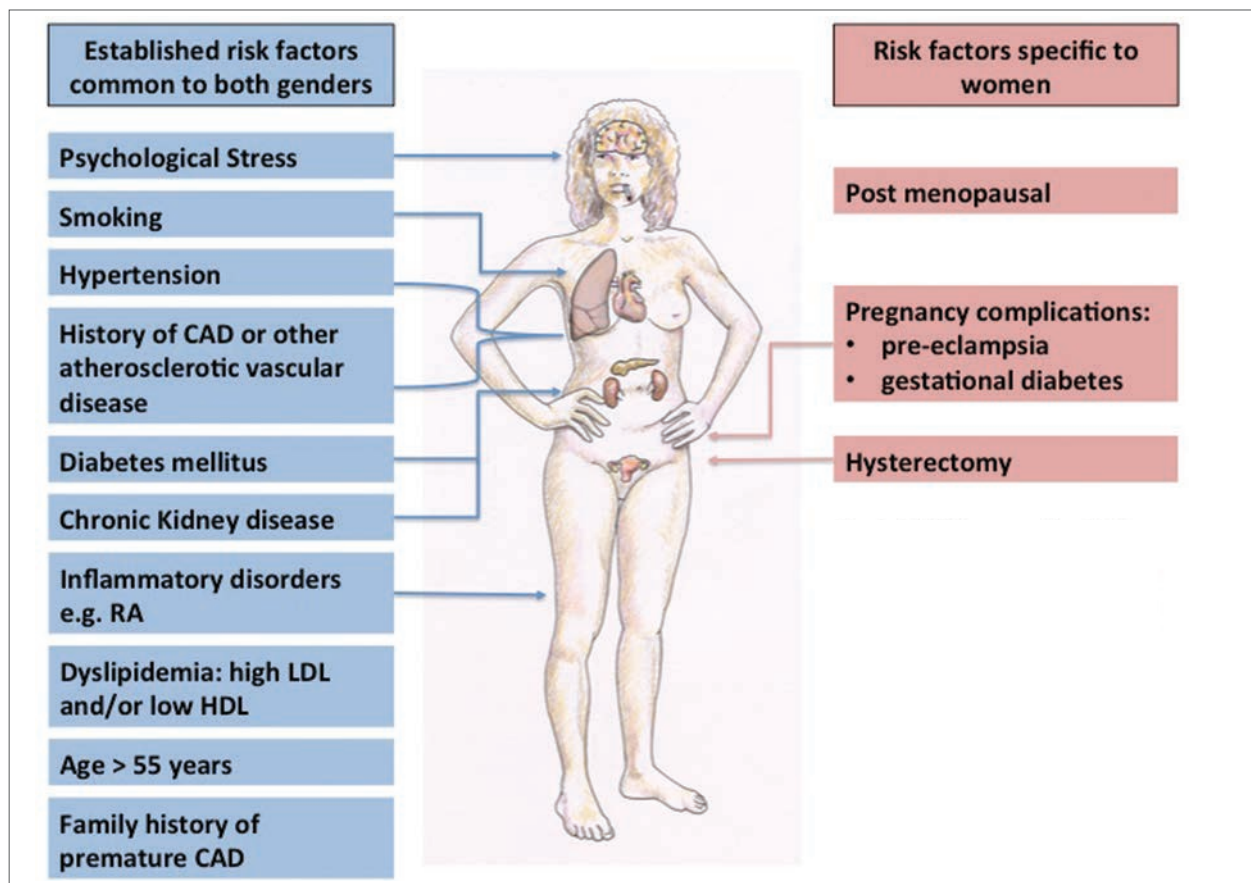


FIGURE 1

Risk factors for CVD which are common to both men and women and those specific to women

What are the sex differences in presentation?

How do risk factors differ between the sexes?

How should women be investigated?



CARDIOVASCULAR DISEASE (CVD) REMAINS THE MOST COMMON CAUSE OF MORTALITY

in women. Approximately 2.8 million women are living with CVD in the UK.¹ Gender-dependent differences in presentation, risk factors and outcomes have been recognised for years. Discrepancies in presentation and outcomes between the sexes are often associated with inequalities in detection, referral and management of CVD.

For many years, the lack of representation of women in clinical trials has led to a paucity of gender-specific evidence and a long-held myth that CVD is a man's disease. Ischaemic heart

disease in women generally presents about a decade later than in men and usually in the postmenopausal period when the protective effects of oestrogen are attenuated.

Population-based risk reduction in women has not achieved significant improvements in the incidence of CVD compared with men. Between 1979 and 1994 there was a significant decline in the incidence of myocardial infarction (MI) in men and a comparative increase in incidence in older women.² Previous data from the National Health and Nutrition Examination Surveys demonstrated an increase in the prevalence of MI in women in the 35 to 54 age range, while a decline in

prevalence was observed in age-matched men.³ Consequently, in order to reduce mortality rates in women, early and accurate diagnosis of coronary artery disease (CAD) is pivotal.

GENDER DIFFERENCES IN PRESENTATION

Difficulty in evaluating symptoms of ischaemic heart disease in women is well documented and remains challenging because of their atypical nature. Additionally the use of typical angina symptoms in the assessment of females may be imprecise owing to the transposition of symptoms derived from male cohorts.⁴

The pattern of presentation initially »

described by the Framingham Heart Study investigators in the 1980s, demonstrated that women generally develop angina as the initial presentation of ischaemic heart disease and are less prone to presenting with an acute myocardial infarction (AMI) compared with men.^{5,6} In acute coronary syndrome (ACS) women also tend to present more commonly with unstable angina rather than ST-segment elevation myocardial infarction (STEMI).^{7,8}

However, in a study of 246 women and 276 men there were no gender differences in the sensitivity of typical symptoms, defined as chest pain or discomfort, dyspnoea, diaphoresis and arm or shoulder pain, in the diagnosis of ACS.⁹

The main gender difference is that women tend to present less frequently with exertional symptoms of chest pain before an AMI.¹⁰

Differences in presentation tend to be more polarised among younger patients compared with older individuals. In the Euro Heart Survey of more than 10,000 patients, older women (> 65 years)

presented with symptoms comparable with those in men and had a greater frequency of typical angina.¹¹

Almost 40 years ago Diamond and Forrester suggested that when assessed by coronary angiography, for typical or atypical symptoms relating to myocardial ischaemia, women demonstrated lower rates of obstructive CAD compared with men.¹² For example, a 55-year-old man with typical exertional symptoms has a 90% probability of obstructive CAD compared with a probability as low as 55% in a woman of the same age. This evidence supports current data that in women, symptoms of chest pain are less discriminatory in predicting obstructive CAD than in men.¹³

Generally, both men and women with established CVD present with chest pain. However, women also report additional, potentially sex-related, non-specific symptoms, such as fatigue and sleep disturbance, see table 1, below. The presentation may confound the diagnosis, making dismissal of these symptoms as non-cardiac all the more perilous.^{14,15}

RISK FACTORS

Although men and women share classic cardiovascular risk factors the relative importance of each risk factor may be gender specific. For example, the deleterious impact of smoking is greater in women than men, especially in those under 50.^{16,17} Smoking also has biochemical effects on the endothelial wall by downregulating oestrogen-dependent vasodilatation.¹⁸

'The lack of representation of women in clinical trials has led to a paucity of gender specific evidence and a long-held myth that CVD is a man's disease'

Typical risk factors should be considered during assessment of CVD risk and include, age > 55 years, pre-existing CAD, hypertension, dyslipidaemia and diabetes mellitus among others, see figure 1, p11. Risk factors specific to women include postmenopausal status, hysterectomy and complications during pregnancy. Women who develop gestational diabetes mellitus (GDM) or pre-eclampsia more than double their risk of developing CVD later in life.¹⁹

Physical inactivity is a significant risk factor for CVD. The Duke Activity Status Index (DASI) is a risk stratification tool measuring functional capacity and comprises a 12-item questionnaire. Women performing < 4.7 METs (metabolic equivalents) of effort in the form of activities of daily living were subject to a 3.7-fold increased risk of death or non-fatal MI when compared with women who engage in greater levels of activity.²⁰

MENOPAUSAL STATUS AND CVD RISK

Transition to the menopause is associated with a worsening CHD risk profile.^{21,22} After the menopause women may experience an increase in body weight, alteration in fat distribution, centripetal obesity and visceral fat deposition, with an associated increase in other CVD risk factors such as diabetes mellitus.²³

Table 1

Gender differences in symptoms of myocardial ischaemia

Common in both sexes

- Pain, pressure or squeezing in chest
- Radiation of pain to neck, shoulder, back, arm, jaw
- Palpitations
- Difficulty in breathing
- Heartburn, nausea, vomiting, abdominal pain
- Cold sweats, clamminess
- Dizziness

More common in women

- Report milder symptoms
- Sudden onset of weakness, shortness of breath, fatigue, feeling of systemic illness (without chest pain)
- Mild discomfort in back, chest, arm, neck or jaw (without chest pain)

Table 2

Factors affecting accuracy of diagnosis of CVD in women

- Endogenous oestrogen in premenopausal women may cause ST-segment changes resulting in false-positive exercise tolerance tests
- Angina and ischaemia vary with the menstrual cycle
- Inability to reach adequate heart rate in exercise tolerance tests or stress testing may impede diagnosis of ischaemia. If > 5 METS cannot be achieved then pharmacological stress testing should be used
- The lower prevalence of disease in premenopausal women results in a lower accuracy of stress testing when compared with men
- *Resting ST-T wave changes*
Reduces the accuracy of identifying changes at peak stress
ACC/AHA guidelines recommend cardiac imaging in individuals with resting ST-T wave changes on the ECG
- *Lower QRS voltage*
Affects the diagnostic accuracy of investigations in women

ACC = American College of Cardiology AHA = American Heart Association MET = metabolic equivalent

Diabetes in particular is a potent risk factor in women, demonstrated by a meta-analysis of 37 studies and almost 450,000 patients which found a 50% greater relative risk of fatal CHD compared with men with the disease.²⁴ This substantial gender difference in mortality is linked to a more adverse risk factor profile, smaller coronary vessel diameter and often inadequate treatment of diabetes in women.

‘Symptoms of chest pain are less discriminatory in women than men for predicting obstructive CAD’

As oestrogen production diminishes in aging women, systolic blood pressure tends to increase, modulated by the increase in plasma-renin activity.²⁵⁻²⁷ Additionally, salt sensitivity and sympathetic drive are increased in postmenopausal women.

Over the age of 75 isolated systolic hypertension is 14% more prevalent in women than men and a significant cause of morbidity due to left ventricular hypertrophy, diastolic heart failure and cerebrovascular disease.²⁸

‘Diabetes is a potent risk factor for CHD in women’

The risk of hypercholesterolaemia in younger women is lower compared with men. However, after the menopause women have a more adverse lipid profile, total cholesterol and low-density lipoprotein (LDL) levels increasing by 10% and 14% respectively without significant change in high-density lipoprotein levels.^{21,29} Postmenopausal re-evaluation of

lipids may be an important consideration in women with a borderline premenopausal profile. Over the age of 65 mean LDL is higher in women compared with men but LDL reduction with statins has been shown to reduce CHD mortality to a similar extent.³⁰

GENDER DIFFERENCES IN MANAGEMENT

Underestimation of cardiovascular risk in women results in delayed or even missed diagnosis of CVD. Focusing on investigations which detect severe coronary stenosis is unlikely to yield accurate diagnoses as women have a lower prevalence of obstructive CAD but have greater symptom burden and functional impairment, see table 2, opposite. The management of stable angina in men and women remains similar, and includes lifestyle modifications, anti-anginal medications and pharmacological secondary prevention, revascularisation and rehabilitation.³¹

Cardiac investigations

The exercise ECG is of limited use in the evaluation of chest pain, owing to lower diagnostic accuracy for CAD in women compared with men (sensitivity and specificity around 60-70% vs 80% respectively).^{32,33} This is partly due to gender-related difficulties in reaching an adequate level of exercise (> 5 METs) required to diagnose inducible ischaemia.²⁰ Hormonal variations may also contribute to false-positive rates in premenopausal women and hormone replacement therapy may cause false-negative results due to vasodilatory properties.³⁴

Exercise stress echocardiography provides more definitive results than exercise ECG. However, pharmacological stress testing is also an accurate diagnostic technique and is preferred for diagnosing CAD in females with lower exercise capacity.³⁵ Stress echocardiography using dobutamine has a sensitivity and

specificity of 85% and 75% respectively for detecting CAD.^{10,20}

Single photon emission computed tomography, a nuclear imaging technique used to evaluate stress-induced myocardial perfusion defects, is also highly accurate. However, image quality is affected by breast tissue and obesity which may result in false-positive results in women.

‘Women who develop GDM or pre-eclampsia more than double their risk of CVD later on’

In the detection of obstructive CAD, CT coronary angiography has similar diagnostic accuracy in detecting $\geq 50\%$ and $\geq 70\%$ coronary stenosis in both sexes.³⁶ Of note, in women over 55 years with intermediate risk for CHD, the lack of coronary calcium has a high negative predictive value (99%).³⁷

MICROVASCULAR ANGINA

This term refers to patients with symptoms of angina and abnormalities on stress testing, despite normal coronary arteries on angiography, with women more affected than men. In a study of 886 patients presenting with chest pain and subsequently undergoing coronary angiography, women were five times as likely to have normal coronary arteries compared with men.³⁸ However, the same risk factors causing atherosclerosis may cause microvascular disease and low oestrogen levels in women have also been implicated. Treatment is based on symptom control with calcium channel blockers and oral nitrates.

STRESS CARDIOMYOPATHY

Stress (Takotsubo) cardiomyopathy is triggered by intense, unexpected emotional or physical stress and is characterised by transient apical systolic dysfunction or ballooning of the left ventricle, see figure 2, left. Presentation is usually similar to AMI with ST segment elevation on the ECG and raised cardiac troponin levels. However, there is no obstructive coronary disease and the observed regional wall motion abnormality is not limited to the territory supplied by a single coronary artery. The syndrome predominantly affects postmenopausal women and in a study of 1,750 patients from 26 centres, almost 90% were women with a mean age of 66.4 years.³⁹ »

FIGURE 2
Left ventriculogram demonstrating the left ventricular ‘ballooning’ seen in Takotsubo cardiomyopathy

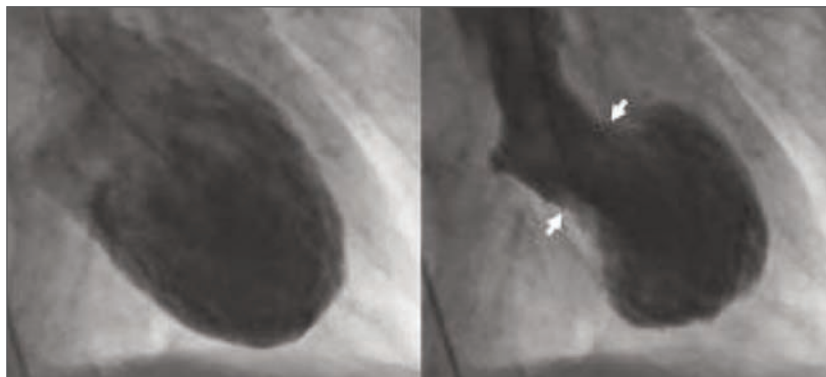


Table 3**American Heart Association guidance for the prevention of CVD in women²²****Lifestyle changes**

- Weight control
- Management of hypertension
- Increased exercise
- Alcohol moderation
- Dietary advice

Encourage **smoking cessation** with advice and cessation therapy

Dietary modification

- Eat oily fish at least twice a week
- Limit saturated fat intake

Aspirin

Consider low-dose therapy in women over 65 if benefits outweigh risks

Hormone replacement therapy and selected oestrogen receptor modulators are not recommended

Antioxidant supplements

e.g. vitamins C and E should not be used for primary/secondary prevention of CVD

The pathogenesis is not fully understood but catecholamine toxicity, microvascular dysfunction and coronary artery spasm have all been highlighted as possible mechanisms. Familial cases raise the suspicion of a genetic component to predisposition, however more convincing is the finding that 56% of sufferers had a psychiatric or neurological disorder compared with 26% of patients with ACS.³⁹

GENDER-DEPENDENT OUTCOMES

The Framingham Heart Study⁶ reported that women with angina had better outcomes and fewer adverse events e.g. AMI, than males. However, more recent data suggest that both men and women presenting with stable angina are subject to increased mortality when compared with the general population.⁴⁰ Therefore stable angina is no longer viewed as a benign condition in women. Evidence to support this comes from the Euro Heart Survey of Stable Angina demonstrating that during the one year follow-up period, women had double the risk of death or non-fatal AMI compared with men.⁴¹

It seems that subgroups of CVD have varying outcomes. Women presenting with STEMI have worse outcomes compared with men.⁴² However, in those presenting with NSTEMI no differences in outcome were demonstrated.⁴³

The pathogenesis of CVD may explain the differences in outcomes. Women with unstable angina are more likely to have non-obstructive CAD compared with men, and less extensive disease correlates with a better prognosis.⁷

In contrast, women presenting with STEMI, where the process of acute thrombus formation secondary to ruptured plaque results in total occlusion of their comparably smaller vessels, have a poorer prognosis.⁴⁴

Women who present with AMI at a young age (< 50 years) have a worse prognosis compared with age-matched male counterparts.⁴⁵ This is highlighted by a large study of more than 50,000 patients who underwent coronary artery bypass grafting between 1993 and 1999, a higher mortality rate was demonstrated among women under the age of 50 when compared with men (3.4% vs 1.1%).⁴⁶ This trend tends to diminish with increasing age.

'Diagnostic procedures and secondary prevention are not applied in women with the same intensity'

IMPROVEMENTS IN THE MANAGEMENT OF WOMEN

In the past, clinical trials have mainly recruited men making it difficult to determine any advantages specific to women. Despite similar recommendations for men and women, it has been well documented that diagnostic procedures and secondary prevention are not applied in women with the same intensity. Once a diagnosis of CVD is made the mainstay of treatment in women should be secondary prevention.

Medical management affects men and women in different ways and should therefore be tailored to gender. For example, beta-blockers have been found to provide greater survival benefit in women with AMI than in men.⁴⁷

The American Heart Association

(AHA) guideline for the prevention of cardiovascular disease in women (2011) highlights the importance of lifestyle modification, smoking cessation and dietary intake in order to reduce morbidity and mortality secondary to CVD, see table 3, left.²² This guidance should inform national strategies for the prevention of CVD in women.

Further studies are required before sex specific guidelines can be robustly and reliably utilised.

CONCLUSION

There are significant differences in the presentation, response to treatment and outcomes between men and women. In 2007, the annual mortality in women secondary to CAD was 4.7 times that of breast cancer.⁴⁸ CVD in women continues to be a major public health concern owing to the difficulties facing physicians in identifying associated symptoms.

In addition, the general attitude that women are somehow protected against CVD compared with men makes the management of CVD in women all the more challenging. The degree of variation between the sexes is not yet known and whether these discrepancies are related to pathophysiology or merely differences in the detection of CVD is yet to be clarified. Ideally, an understanding of these variables will lead to gender specific prevention, identification and management of CVD in women with a beneficial effect on morbidity and mortality.

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key points

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Cardiovascular disease (CVD) remains the most common cause of mortality in women. In 2007, the annual mortality in women secondary to CAD was 4.7 times that of breast cancer. Around 2.8 million women are living with CVD in the UK. Data from the National Health and Nutrition Examination Surveys demonstrated an increase in the prevalence of MI in women aged 35 to 54, while a decline in prevalence was observed in age-matched men.

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Although men and women share classic cardiovascular risk factors the relative importance of each risk factor may be gender specific. The deleterious impact of smoking is greater in women than men, especially in those under 50. Diabetes is a more potent risk factor for fatal CHD in women than men. Risk factors specific to women include postmenopausal status, hysterectomy and complications during pregnancy. Women who develop gestational diabetes mellitus or pre-eclampsia more than double their risk of CVD later in life. Transition to the menopause is associated with a worsening CHD risk profile. After the menopause women may experience an increase in weight, alteration in fat distribution and an increase in other CVD risk factors such as diabetes. They may also have a more adverse lipid profile, total cholesterol and LDL levels increasing by 10 and 14% respectively without significant change in HDL levels. As oestrogen production diminishes, systolic BP tends to increase.

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Useful information

American Heart Association guideline
<http://circ.ahajournals.org/cgi/content/full/123/11/1243>

British Heart Foundation
www.bhf.org.uk/heart-health/living-with-a-heart-condition/womens-room/your-heart-health

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