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PEER REVIEWED FEATURE
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Women with heart disease: are they overlooked?

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Key points

- It is important to raise public and physician awareness of heart disease in women.
- Most women in Australia have two or more modifiable cardiovascular risk factors.
- Women with diabetes are a high-risk group for cardiovascular disease and warrant close follow up.
- It is important to eliminate gender bias through timely referral, appropriate investigation and application of evidence-based treatments.
- Women derive a clinical benefit from secondary prevention similar to men but remain undertreated and, ultimately, women with coronary heart disease have a worse prognosis than men.
- There is a need for increased recruitment of women in clinical trials on cardiovascular disease.

Heart disease remains the major killer of women in Australia. Many of these deaths are preventable through risk-factor modification and early detection of the disease.

Cardiovascular disease (CVD) refers to several conditions affecting the heart and blood vessels, including coronary heart disease (CHD), heart failure, stroke and peripheral vascular disease. This article focuses on CHD in women in Australia, which is predominantly caused by atherosclerotic coronary artery disease and usually presents as either angina or myocardial infarction (MI).

CHD has traditionally been viewed as a 'man's disease' and relatively few women realise that heart disease and stroke pose the greatest risk to their health.[1] There is often a public misconception that breast cancer represents the major threat to a woman's life, when in fact CHD kills four times as many women in Australia as breast cancer.[2] In 2006, CHD claimed 10,800 female lives and CHD was, by far, the leading specific cause of death for both sexes, accounting for about one in six deaths (Figure 1).[2] Many of these deaths were premature, and CHD was the leading cause of premature death in women in 2003.[2] Failure of women to appreciate the significance of their lifetime risk of CHD is one of the major barriers to effective prevention strategies through early identification and modification of cardiovascular risk factors.

PREVALENCE OF CARDIOVASCULAR RISK FACTORS

Most premature deaths due to CHD are preventable. The 2001 National Health Survey found that over 90% of women had at least one modifiable cardiovascular risk factor, 50% of women had two or three risk factors and 15% had four or more.[2] It is the interplay of multiple risk factors that significantly increases a woman's risk of CHD. Doctors should focus on an individual's absolute risk of developing CHD when planning treatment strategies. There are a number of CVD risk calculators available (for example, see: www.cvdcheck.org.au).[3]

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Advancing age

Women in Australia are currently still living longer than men, although the gap is closing. Almost 60% of the population over 75 years of age are female and this percentage rises further with increasing age.[2] In women, the incidence of CHD significantly increases from the age of 60 years, often lagging 10 years or more behind men with CHD, the so-called 'protective effect'.[4,5] As Australia's population ages, the burden of CHD is certain to escalate, especially in women.

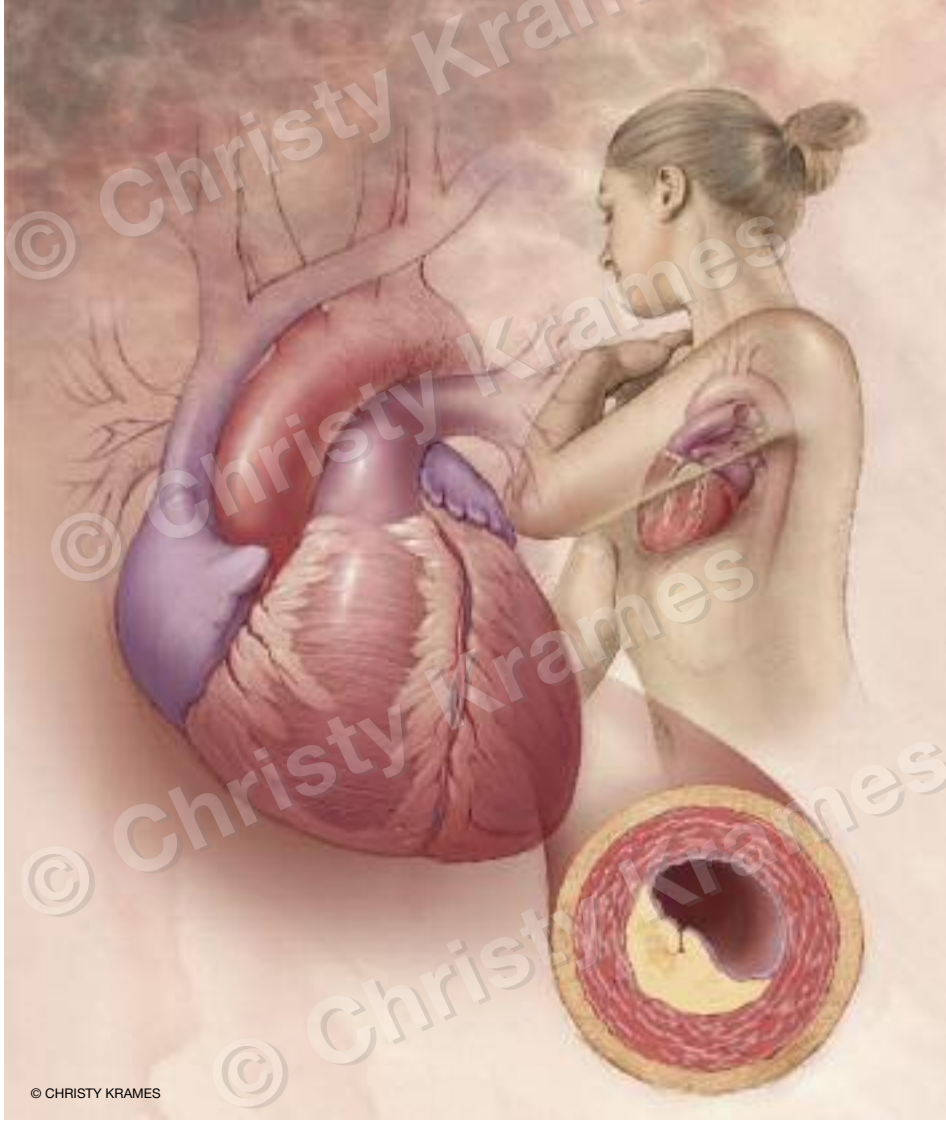
Smoking

Although the overall incidence of smoking is in decline, 15% of women in Australia continue to smoke daily.[2] Smoking just one to four cigarettes per day results in a twofold increase in the risk of fatal CHD in women and smoking 25 cigarettes or more per day increases the risk more than fivefold.[6] After one year of smoking cessation, the risk of CHD is halved and after two to six years of smoking cessation, the risk is equivalent to a nonsmoker's risk.[2]

Women taking an oral contraceptive metabolise nicotine faster than men, and earlier studies have found that use of current oral contraceptives increased the risk of MI, especially in women who smoked.[7] Recent studies have not found use of oral contraceptives to be an independent risk factor for MI and there are no data available for the newest generation formulations.[7] American guidelines suggest using alternative forms of contraception for women who are over 35 years of age and smoke.[7]

Diabetes

Diabetes is a growing problem in Australia and up to 7% of women in Australia have type 2 diabetes.[2] Diabetes significantly increases morbidity and mortality from CHD, more so in women than in men. In type 1 diabetes, there is a complete loss of the 10-year protective effect conferred by the female sex, whereas in type 2 diabetes the sex difference is markedly attenuated.[8] This needs to be considered when assessing younger women with diabetes for possible CHD, especially when using risk calculators to determine pretest probability.



Hypertension

Hypertension is a major risk factor for CHD, stroke, heart failure, peripheral vascular disease and renal failure and it is the equal biggest contributor to the overall burden of disease in women.[2] Of women in Australia, 27% have hypertension and the prevalence increases significantly with age; almost half of women in their fifties and three-quarters of women in their mid-seventies have high blood pressure.[2]

Hypercholesterolaemia

Almost 50% of women in Australia have high cholesterol levels. Total cholesterol levels peak in women between 55 and 65 years of age and hypercholesterolaemia becomes more prevalent in women than in men at this age.[1,2] In both genders, the risk often starts early, with more than one-quarter of young people aged 25 to 34 years having high cholesterol levels.[2]

Obesity, diet and exercise

Despite an abundance of fresh food and the 'great outdoors', 93% of women in Australia

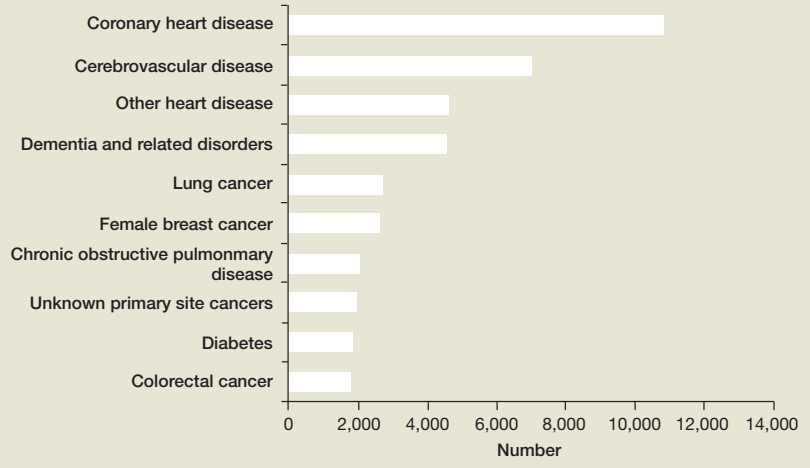


Figure 1. Leading specific causes of death for females of all ages, 2006.*

* Reprinted with permission from the Australian Institute of Health and Welfare.[2]

do not consume the recommended intake of fruit and vegetables, 76% do not exercise regularly and consequently 55% are overweight or obese.[2] Using waist circumference data, an indicator of excess abdominal weight, 64% of females aged 18 years and over are at an increased risk of CHD.[2] Women are more likely than men to be sedentary or have low levels of physical activity across almost all age groups.[2] Regular physical activity reduces the risk of CHD both directly and indirectly through its positive effects on other risk factors, including blood pressure, body weight and type 2 diabetes.

PRESENTATION OF CHD

Compared with men, women are more likely to present with unstable angina and less likely to present with acute MI.[4] In cases of acute MI, women more commonly present with Q-wave MI and have less prominent ST-segment elevation.[4]

Women with CHD are more likely to experience atypical symptoms. Approximately one-third of patients with acute coronary syndromes (ACS) do not experience chest pain or discomfort and this is more common in women than in men.[4] Women also tend to report a greater number of associated symptoms, such as jaw or back pain, dyspnoea, paroxysmal nocturnal dyspnoea, nausea, anorexia, indigestion, dizziness, weakness, fatigue, cough and palpitations.[4]

Women, especially those aged older than 65 years, wait longer than men before seeking treatment for ACS.[4,9,10] The longest phase of delay in ACS continues to be the time from symptom recognition to the decision to seek care.[9] A meta-analysis reported that the most significant reasons for treatment delay in women were atypical symptoms, failure to correctly attribute symptoms to the heart, perceived severity and seriousness of symptoms, confusion of acute symptoms with other chronic illness, low self-perceived vulnerability to heart attack and utilisation of other coping mechanisms.[10] Treatment delay could be substantially reduced by increasing public awareness of heart disease in women and educating women in symptom recognition and the importance of a timely presentation. The campaign 'Go Red for Women' has recently been launched by the National Heart Foundation to help address this.

INVESTIGATION OF SUSPECTED CHD

Exercise ECG

The accuracy of exercise ECG testing is reduced in women compared with men. A large meta-analysis found that the sensitivity and specificity of exercise ECG testing in women were 61% and 70%, respectively; this compares with 72% and 77%, respectively, in men.[5] This is because women are more likely to have an abnormal baseline ECG and tend to present in older age with more comorbidities.[4,11] Physical factors such as leg pain, orthopaedic problems and deconditioning limit maximal capacity exercise and therefore reduce the accuracy of the test. The diagnostic accuracy of exercise ECG testing can be improved by integrating multiple parameters. Exercising for longer than six minutes, achieving a heart rate of more than 150 beats per minute and an ST recovery time of less than one minute identifies women at low risk and helps improve the positive predictive value of the test.[12]

If possible, cardiac imaging should be used for all patients with a high pretest probability of CHD. Imaging is also recommended for any patient who is unable to exercise adequately and for those with an abnormal baseline ECG, such as a widespread resting ST-segment depression, complete left bundle-branch block (LBBB), ventricular paced rhythm or pre-excitation. Exercise ECG does have a high negative predictive value in women with a low pretest probability, at the expense of a higher false-positive rate.[5] However, in many cases, patients with a low pretest probability may not require any investigation.

Stress echocardiography

Stress echocardiography has a mean sensitivity of 81% (89% in multivessel disease) and a specificity of 86%.[5] It is equally accurate for women and men and has the significant benefit of no ionising radiation. It also provides important structural information such as left ventricular

Figure 2. A women undergoing a stress echocardiogram test.

function and valve function. Imaging can be limited in severely obese patients or in people with hyperinflated lungs. In patients who cannot exercise, dobutamine, a synthetic catecholamine, is the preferred pharmacological agent because it is more effective than vasodilators in producing stress-induced regional wall motion abnormalities.[13]

Stress echocardiography is appropriate in patients with an intermediate or high pretest probability of CHD and in patients with a positive exercise ECG. It is particularly useful in young women in whom excess radiation should be avoided (Figure 2).

Myocardial perfusion imaging

Myocardial perfusion imaging (MPI; also known as a thallium or sestamibi scan) has a powerful positive predictive value in women with regard to the development of subsequent cardiac events, including death.[5] In the past, artefact caused by breast tissue and smaller heart size limited the accuracy of MPI in some women. However, the evolution of newer agents, such as technetium and ECG-gating, has resulted in high diagnostic and prognostic accuracy. Some studies report a sensitivity and specificity as high as 91% and 86%, respectively.[5] If a patient is unable to exercise adequately or has a LBBB, a vasodilator agent (such as dipyridamole) is often administered to increase diagnostic accuracy.

Markers of high-risk CHD include post-stress left ventricular dilation or reduction in left ventricular ejection fraction to less than 35% and increased lung thallium uptake. The main disadvantage is ionising radiation. In a large US cohort, MPI accounted for three-quarters of the cumulative effective dose of radiation from cardiac imaging procedures, including coronary angiography.[14] MPI is appropriate in patients with an intermediate or high pretest probability of CHD and in those with a positive exercise ECG test. It is particularly useful for people who cannot exercise, morbidly obese patients and for those with a LBBB.

CT coronary angiography

Coronary artery calcification scoring has largely been replaced by multi-slice CT coronary angiography (CTCA), an emerging imaging tool that is becoming increasing available in Australian tertiary hospitals. It has a high sensitivity and specificity and a negative predictive value of 93%.[15] It offers the potential for rapid assessment of chest pain in the emergency department and earlier discharge if the scan is negative, without awaiting cardiac enzyme results. The main disadvantages are contrast administration and radiation exposure. There is a 'non-negligible' lifetime associated risk of cancer, which is significantly higher in women and young patients. A recent study reported that cancer risk estimates for standard CTCA varied from one in 143 for a 20-year-old woman to one in 3261 for an 80-year-old man.[16] Its precise role in the assessment of CHD is still being established.

Perfusion cardiac magnetic resonance imaging

Perfusion cardiac magnetic resonance imaging is still in early development, but it appears superior to MPI.[17] It is equally accurate in women and men, and is not associated with radiation exposure. However, the considerable set-up cost and longer scanning time may limit its widespread use in Australia.

Coronary angiography

Coronary angiography remains the gold standard for the diagnosis of CHD (Figure 3). It is both diagnostic and therapeutic and it is the procedure of choice in most cases of acute MI, especially ST-elevation MI (Figure 4). ACS without angiographic obstruction of the large coronary arteries is more commonly observed in women than in men.[4] Rates of peripheral vascular complications and bleeding are more common in women,[18] possibly a result of smaller vessel size and lower body weight, leading to excessive doses of antithrombotic agents.

GENDER DISPARITY

Multiple studies suggest a gender bias exists in the investigation and treatment of women with heart disease. The Australian Institute of Health and Welfare recently reported that at all age ranges, women were less likely than men to

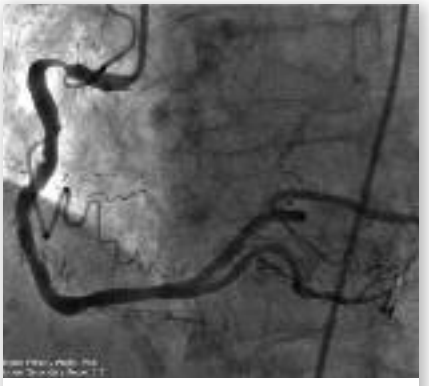


Figure 3. Coronary angiogram demonstrating a proximal stenosis of the right coronary artery.

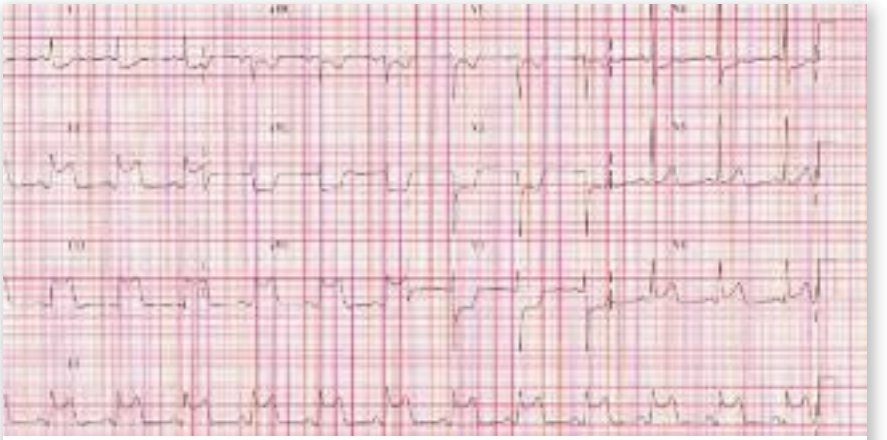


Figure 4. ECG demonstrating inferior ST-elevation myocardial infarction.

be admitted to hospital with CHD, and when women were hospitalised with heart disease, they were less likely to be comprehensively investigated and treated.[2] In a non-ST-elevation MI cohort, women were less likely to have an ECG performed within 10 minutes of hospital presentation, were less commonly cared for by a cardiologist as an inpatient, and less likely to receive evidence-based treatments.[19] The Euro Heart Survey of stable angina found that women were less likely to be referred for exercise stress testing and less likely to undergo coronary angiography, even after adjustment for the results of noninvasive tests.[20] Women with confirmed CHD were also less likely than men to be revascularised and less likely to receive optimal secondary preventive therapy. Yet, the women in this study were twice as likely to suffer death or nonfatal MI during the one-year follow-up period.

Some authors argue that observed gender differences are strongly related to age and comorbidities. After adjusting for age in one acute MI cohort, gender differences remained significant only for thrombolysis and exercise stress testing.[21] In our view, CHD in women is frequently overlooked, under-investigated and suboptimally managed compared with CHD in men.

Clinical trials are another source of gender disparity in CHD. Women have been vastly under-represented in cardiovascular clinical trials to date, often comprising less than 30% of study cohorts, although this is improving.[8] In addition, as many as 50% of trials do not report the analysis of the results by gender, resulting in a paucity of evidence-based data to guide treatment in women.[8,22]

ANATOMICAL AND PHYSIOLOGICAL DIFFERENCES

The coronary vessels of women are often smaller than those of men,[11] which makes them more difficult to revascularise percutaneously as well as surgically, and the risk of future restenosis is increased. Women tend to have a larger and less atherogenic LDL particle size than men.[23]

An intravascular ultrasound study found that women with CHD have less atherosclerotic plaque in their coronary arteries than men with CHD, despite having more cardiovascular risk factors and higher LDL and triglyceride levels.[24] However, following intensive treatment, women derived the same benefit as men in regards to plaque regression.[24] Women also tend to have a lower body mass index, higher proportions of body fat, smaller organ size, lower glomerular filtration rates and a fluctuating percentage of tissue water depending on the menstrual cycle, all of which can alter the therapeutic response to various drugs.[22] In addition, women generally have a slightly faster resting heart rate, a longer corrected QT interval and a 50 to 70% greater risk of experiencing an adverse drug reaction.[22]

The effect of hormonal differences on CHD in women remains poorly understood. Oestrogen inhibits the renin-angiotensin system (RAS), leading to lower ACE activity in premenopausal women, which may contribute to the cardioprotective effect that younger women benefit from.[22] However, the Women's Health Initiative did not demonstrate a cardioprotective effect in postmenopausal women receiving oestrogen alone, and women receiving oestrogen plus progestin may be at an increased risk of CHD.[25] In view of this, hormone replacement therapy is not recommended for primary cardiac protection alone.

TREATMENT OF CHD

Aspirin

The use of aspirin for primary cardiovascular prevention remains controversial. A meta-analysis found aspirin reduced the risk of ischaemic stroke but not MI in women, and reduced the risk of MI but not stroke in men.[26] Bleeding risk was significantly increased in both

genders. For secondary prevention of CVD, a net clinical benefit of aspirin has been well established for both women and men.[22]

Statins

The use of statin therapy for primary prevention of cardiovascular disease in women is still debated. A recent meta-analysis demonstrated a reduction in primary CVD events in women;[27] however, several earlier analyses have contradictory findings.[28] In patients with established CHD, statins are potent first-line lipid-lowering agents and women seem to derive a similar benefit from them as men.[22,28] Despite this, statins are employed less frequently in women requiring secondary prevention.[22] In high-risk patients with existing CHD, the National Heart Foundation and Cardiac Society of Australia and New Zealand recommend target total cholesterol levels of less than 4.0 mmol/L, increased emphasis on reducing LDL cholesterol to less than 2.0 mmol/L, HDL cholesterol levels of more than 1.0 mmol/L and triglyceride levels of less than 1.5 mmol/L.[29]

Beta blockers

Beta blockers reduce angina symptoms, reduce arrhythmias and have mortality benefits in patients with MI and heart failure. A meta-analysis concluded that the mortality benefit of metoprolol following MI was comparable in woman and men.[22] Significantly higher plasma levels of metoprolol have been observed in women owing to slower drug metabolism,[22] which warrants careful attention when initiating drug therapy.

RAS blockers

ACE inhibitors are indicated for left ventricular dysfunction post-MI, and the favourable effects on prognosis and reduction in hospitalisation rates appear to be similar in men and women.[22] Angiotensin II receptor blockers are second-line agents for left ventricular dysfunction if ACE inhibitors are not tolerated. ACE inhibitor-induced cough occurs twice as frequently in women.[22] Both RAS blockers are effective antihypertensive agents, irrespective of gender.[22]

Percutaneous coronary intervention

Women more often than men need urgent coronary intervention because of late presentation.[11] The risk of adverse events during and after percutaneous coronary intervention is greater in women than in men, despite similar procedural success rates.

A Canadian group demonstrated that women have a markedly increased early risk for mortality following both percutaneous and surgical revascularisation. However, by 12 months the risk for women had decreased to a level equivalent to that for men.[30] A significant gender difference was not observed in patients undergoing conservative therapy.

Coronary artery bypass grafting

Coronary artery bypass graft (CABG) surgery is indicated for patients with significant lesions of the left main coronary artery and also for those with multivessel disease, especially in patients with diabetes.

Despite advances in myocardial protection and surgical technique, female sex remains a risk factor for in-hospital morbidity and mortality. On average, in-hospital mortality is doubled and periprocedural stroke and bleeding occur more frequently in women compared with men.[11] Interestingly, younger women undergoing CABG are at a significantly higher risk of in-hospital death compared with men and this sex difference is attenuated with increasing age.[11]

LONG-TERM PROGNOSIS

Women with CHD have a significantly worse in-hospital and long-term prognosis than men. Older age, more comorbidities and generally smaller body surface area are all contributing factors. It is not clear whether gender itself is an independent predictor of risk.[1,11,31]

SUMMARY

Heart disease remains the major killer of women in Australia. Many of these deaths are preventable through risk-factor modification and earlier detection of disease. Patient factors should be considered when selecting an appropriate screening test for CHD. Women derive a similar clinical benefit to men from secondary prevention but remain undertreated and, ultimately, women with CHD have a worse prognosis than men. MT

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

Women and heart disease

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