

Coronary artery disease in women

SUMMARY

Cardiovascular disease is the leading global cause of death in women but remains underdiagnosed and undertreated.

Health professionals play an important role in improving the heart health of Australian women. Routine heart health checks should be offered to all women 45 years of age and older and to all Aboriginal and Torres Strait Islander women 30 years of age and older.

Cardiovascular risk assessment in women must include traditional and sex-specific risk factors, including their pregnancy history and early-onset menopause.

Women with pregnancy-related hypertensive and metabolic disorders have an increased long-term cardiovascular risk and require close monitoring.

Women with acute coronary syndrome may not experience classical chest pain. More often, they experience cardiovascular events in the absence of obstructive coronary disease and have poorer cardiovascular outcomes.

The recognition of sex-specific differences and more sex-specific trials are key to improving clinical outcomes.

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Introduction

Cardiovascular disease, which encompasses heart disease, stroke and peripheral vascular disease, is the leading cause of illness and death in women worldwide. Biological and physical differences, such as a smaller body surface area, smaller coronary vessel size and sex hormone-mediated factors in women, are exacerbated by sociocultural factors and contribute to differences in the prevalence, presentation and natural history of cardiovascular disease between the sexes. Women with cardiovascular disease experience delays in diagnosis, are less likely to be treated in line with guidelines and standards, and have higher complication rates and worse outcomes than men. Women are significantly under-represented in clinical trials, and sex-specific diagnostic and management strategies are not included in current clinical guidelines.

Epidemiology

Three out of every 10 female deaths in Australia are due to cardiovascular disease, including coronary artery disease.¹ It is estimated that between the ages of 45 and 64 years, one in nine women will develop some form of cardiovascular disease, which increases to one in three women after the age of 65 years.^{2–4} Indigenous Australian women are particularly at risk, often at a younger age. In 2016, indigenous women aged 25 years and older experienced an acute coronary event in the form of myocardial infarction or unstable angina at a rate of 617 per 100,000 population. This

is 3.8 times more likely than in other Australian women.⁵ Positively, the mortality rates of coronary artery disease have been declining in Australia in recent decades. From 2006 to 2016, the rate fell by 46% for women (from 78 to 44 per 100,000 population) and by 40% for men (from 135 to 84 per 100,000 population).⁵ Further, between 2001 and 2016, the prevalence of acute coronary events (myocardial infarction and unstable angina) in Australian women fell by 57% (from 465 to 215 events per 100,000).⁵ However, the rates of decline are lower in women under the age of 55 years, with a rise in strokes and myocardial infarcts.¹

Cardiovascular risk factors

Various traditional and sex-specific risk factors increase the risk of cardiovascular disease in women.

Traditional risk factors

Traditional risk factors are more often under-recognised and undertreated in women than in men and affect the risk of cardiovascular disease differently between the sexes (Box 1).^{4,6–18}

Sex-specific risk factors

Several female-specific risk factors increase the risk of cardiovascular disease in women.

Hormonal contraceptives

Combined hormonal contraceptives are associated with a 12-fold increase in the risk of acute myocardial infarction in women with hypertension¹⁹ and should

Box 1 Traditional cardiovascular risk factors in women**Hypertension**

The impact of hypertension on the risk of developing ischaemic heart disease seems consistent across the sexes.⁶

Although sex differences in the incidence of hypertension have not been found,⁶ hypertension is undertreated in women,⁷ leading to heart failure with preserved ejection fraction.⁸

Dyslipidaemia

The ratio of total cholesterol to high-density lipoprotein cholesterol is more powerfully associated with acute myocardial infarction in women than in men.⁴

Diabetes

Diagnosis occurs at a higher body mass index, older age and more advanced stage of disease progression in women than in men.

Obesity

The Framingham Heart Study showed that the excess risk of cardiovascular disease from obesity was 64% in women versus 46% in men.⁹

Smoking

Tobacco use confers a 25% increase in the risk of developing coronary artery disease compared to that in men.¹⁰

Systemic inflammation and auto-immune disorders

These more commonly affect women and cause endothelial dysfunction and the acceleration of atherosclerosis, resulting in an increased risk of cardiovascular disease.¹¹

Sedentary lifestyle

The increase in the risk of cardiovascular disease risk is greater in women (particularly older women) as they are more sedentary than men.^{12,13}

Psychosocial

Physical and psychological abuse affects 15–71% of women and contributes to depression.^{14,15,16} Increased substance abuse including tobacco and alcohol in women who report partner violence independently contributes to an increased cardiovascular risk.^{17,18}

be avoided in this subgroup. Progestogen-only contraceptives should be considered in women with an increased risk of acute myocardial infarction. Prior use of hormonal contraceptives does not increase the risk of subsequent cardiovascular disease.²⁰

Pregnancy-related disorders

Hypertensive and metabolic disorders of pregnancy are also independently associated with an increased risk of maternal cardiovascular disease.²¹ These include gestational hypertension, pre-eclampsia, eclampsia and placental abruption. Early onset (<34 weeks) and severe degrees of pre-eclampsia confer a particularly increased risk of maternal cardiovascular disease in later life,²² potentially due to resultant endothelial dysfunction, which persists for many years after an affected pregnancy and is linked to atherosclerosis.²³ Women with gestational diabetes have an increased risk of subsequent cardiovascular disease, and more than 50% will go on to develop chronic type 2 diabetes mellitus.²⁴

Menopause

Following menopause, the risk of cardiovascular disease rises substantially. This is possibly related to a sharp, sustained increase in low-density lipoprotein cholesterol around the time of the final menstrual period.²⁵ Lower concentrations of oestrogen and higher concentrations of androgen contribute to this increased risk.²⁶ Premature menopause increases the risk of cardiovascular disease before the age of 60 years.²⁷

Menopausal hormone therapy

Randomised controlled trials have not shown any benefit in primary or secondary prevention with the use of hormone replacement therapy. Oestrogen use results in a small but significantly increased risk of cardiovascular events, particularly in women starting therapy 20 or more years after menopause or at least from 70 years of age.²⁸ In women with acute myocardial infarction, menopausal hormone therapy should be discontinued.²⁹

Other hormonal factors

Early menarche (<12 years of age), young age at first birth, a history of miscarriage, stillbirth, preterm birth, low-birthweight babies and hysterectomy are independently associated with an increased risk of cardiovascular disease in later life.³⁰ This is possibly mediated by increased systemic inflammation³⁰ and endothelial dysfunction, which accelerate atherosclerosis.³¹ Polycystic ovarian syndrome is associated with a heightened risk of cardiovascular disease, specifically coronary artery disease.³² The clustering of insulin resistance, obesity and metabolic syndrome, which leads to type 2 diabetes, dyslipidaemia and hypertension, may be causal.³³

Cancer radiotherapy and chemotherapy

Radiation can cause coronary endothelial injury leading to a pro-inflammatory state, the rupture of vessel walls, platelet aggregation, thrombosis and the replacement of damaged intima by myofibroblasts, resulting in vessel stenosis and atherosclerosis.³⁴ Women with a history of breast cancer receiving radiotherapy show a relative 7.4% increase in the risk of cardiovascular events with each gray of radiation exposure.³⁵ Furthermore, for reasons that are unclear, women treated with mantle or mediastinal radiation for Hodgkin lymphoma have a significantly higher cardiovascular event rate and mortality compared to those in men, highlighting the need for increased surveillance.³⁶ Reduced cardiovascular-specific survival has also been reported in women treated with radiation for cervical and uterine cancers.³⁷

Cardiovascular risk assessment

Cardiovascular risk should be assessed differently in men and women (Box 2). The Framingham Risk Score underestimates the risk of cardiovascular disease in women.³⁸ The Reynolds Risk Score³⁹ is best suited for women.⁴⁰ This 10-year cardiovascular risk prediction algorithm for women older than 45 years of age includes two additional risk variables. These are the high-sensitivity C-reactive protein concentration and a parental history of premature coronary artery disease before 60 years of age (Table).

No sex-specific risk factors are included in any available primary prevention risk assessments. Further research that promotes the incorporation of female-specific risk factors in this algorithm would improve the accuracy of cardiovascular risk assessment in women.

Types of coronary artery disease

There are differences between men and women across different types of coronary artery disease.

Coronary artery disease

Obstructive coronary artery disease generally manifests similarly in women and men, with the most common symptom being central chest pain. In women, there is a greater likelihood of chest pain onset at rest, during sleep or when under mental stress. Women also more frequently present atypically with pain in the upper back, arms, neck and jaw, as well as presenting with dyspnoea, diaphoresis, indigestion, nausea, palpitations, dizziness and weakness.⁴¹ Furthermore, the proportion of women aged 55 years and younger presenting with acute coronary syndrome without chest pain is significantly greater than the proportion of men (19% vs 13.7%).⁴² As a result, they are at a greater risk of being discharged home with evidence of acute coronary syndrome compared to men.⁴³

Women with coronary artery disease also more frequently develop symptomatic heart failure than men. This may be due to the impact of co-existent hypertension, an important risk factor for coronary artery disease, which leads to a greater incidence of left ventricular hypertrophy that is less responsive to antihypertensive therapy in women, resulting in diastolic dysfunction and heart failure with preserved ejection fraction.⁴⁴

Ischaemia with non-obstructive coronary artery disease

Ischaemia with non-obstructive coronary disease is a condition due to coronary microvascular dysfunction or epicardial vascular spasm. It is more common in women, especially at 45–65 years of age.⁴⁵ If this

Box 2 Coronary artery disease in women compared to men

Presentation

Similar to men, where most experience central chest pain, but onset is more often at rest

Atypical symptoms more frequent, including pain in the upper back, arms and jaw, and diaphoresis, dyspnoea, indigestion, nausea, dizziness, fatigue and palpitations

Absence of chest pain more often in acute coronary syndrome

Ischaemia and myocardial infarction more often in the setting of non-obstructive coronary artery disease

Takotsubo syndrome a common cause of myocardial infarction

Diagnosis

Reynolds Risk Score more accurate than the Framingham Risk Score

Better prognostic information from CT coronary angiography than from functional testing

Coronary angiography used less often after positive exercise stress test results

Treatment

Statins used less in angina and after myocardial infarction

Similar coronary stent use

Less frequent coronary artery bypass grafting

Table Reynolds Risk Score for cardiovascular risk in women³⁹

Risk factor	Measure
Age	years
Systolic blood pressure	mmHg
Diabetes mellitus	<input type="checkbox"/> Yes <input type="checkbox"/> No
Current smoker	<input type="checkbox"/> Yes <input type="checkbox"/> No
High-density lipoprotein cholesterol	mmol/L
Total cholesterol	mmol/L
High-sensitivity C-reactive protein	mg/L
Parental history of premature coronary artery disease aged <60 years	<input type="checkbox"/> Yes <input type="checkbox"/> No

The Reynolds Risk Score is an online calculator that uses a risk prediction algorithm to predict the 10-year cardiovascular event risk, for myocardial infarction, ischaemic stroke, coronary revascularisation and cardiovascular mortality (<5% = low risk, 5–9% = moderate risk, 10–19% = moderate-to-high risk, ≥20% = high risk).⁴⁰

condition or coronary stenosis is not diagnosed, many women are mistakenly presumed to not have heart disease and are not treated, which increases their risk of adverse cardiac events. A comprehensive meta-analysis has revealed an overall estimated incidence of all-cause mortality or myocardial infarction of 0.98 per 100 person-years in patients with non-obstructive coronary disease compared with 0.2 per 100 person-years in a similarly matched general population. In addition, 50% of patients with non-obstructive coronary disease will experience

repeated episodes of ischaemic chest pain, similar to those with obstructive coronary artery disease, further underscoring the importance of the condition. Functional coronary angiography is needed to evaluate macroscopic resistance, coronary flow reserve and microvascular resistance to confirm the diagnosis that is otherwise missed on routine non-invasive testing.⁴⁶

Myocardial infarction with non-obstructive coronary artery disease

Myocardial infarction with non-obstructive coronary artery disease (MINOCA) is roughly three times more common in women than in men.⁴⁷ This is based on a pooled analysis of 10 studies that recruited both patients with MINOCA and myocardial infarction with obstructive coronary artery disease (MI-CAD).⁴⁸ Furthermore, approximately 25% of patients with MINOCA have ongoing angina, equivalent to the prevalence in patients with MI-CAD.⁴⁷ The pathophysiology is unknown in approximately a quarter of MINOCA cases. Processes involving the epicardial vessels and coronary microvascular disease, which prevent an increase in myocardial blood flow in response to an increased oxygen demand, may be responsible. There may also be an overlap with mild forms of Takotsubo syndrome.⁴⁹

Takotsubo syndrome

Takotsubo syndrome accounts for 7.5% of cases of acute myocardial infarction in women, with 90% of cases occurring in postmenopausal women aged 50–75 years.^{50–52} It is triggered by emotional or physical stress, which is associated with enhanced sympathetic activity. Patients present with chest pain and ECG changes characteristic of acute coronary syndrome but without angiographically obstructive coronary artery disease. These patients have reversible left ventricular ballooning. Cardiac arrest occurs in 5.9% of patients.⁵³

Spontaneous coronary artery dissection

In at least 25% of women aged 60 years or younger, spontaneous coronary artery dissection causes acute myocardial infarction, with conventional risk factors often being absent. It is the most common cause of myocardial infarction associated with pregnancy, primarily occurring in the third trimester or postpartum.⁵⁴ The risk of recurrence is substantial with a pathological process independent of atherosclerotic disease. While strategies to prevent spontaneous coronary artery dissection include avoiding hormonal therapy and future pregnancies, there is currently a lack of evidence that allows for treatment guidelines to be established.

Diagnosis of cardiovascular disease

Women are not referred as often as men for appropriate diagnostic and therapeutic procedures for cardiovascular disease.⁵⁵ A biased view that coronary artery disease preferentially affects men may lead to underestimation of its severity in women, resulting in lower rates of invasive testing and intervention.^{56,57} Such biases may be more extreme in younger patients due to a lower incidence of coronary artery disease in younger women.⁵⁸ Clinicians may also be concerned about the safety of invasive procedures in women.⁵⁹ Women have higher risks of bleeding and vascular complications following percutaneous coronary intervention and surgery, which may lead to a greater reluctance to intervene.^{60,61}

Risk assessment

The presence of diabetes, smoking habits and a family history of premature coronary artery disease are risk factors of cardiovascular disease.⁶² In the presence of these factors, the risk is greater in women than in men.^{56,63,64}

Non-invasive testing

Stress tests, involving either exercise or drugs to mimic the effects of exercise, are used primarily for the diagnosis and risk stratification of obstructive coronary artery disease. Exercise testing is associated with a higher false-positive rate of diagnosis in women than in men due to a lower pre-test probability of the disease.⁶⁵ Exercise echocardiography is often preferred to stress nuclear imaging or CT coronary angiography in women because of concerns about radiation exposure, particularly to the breasts. However, CT coronary angiography may provide greater prognostic information than that provided by functional stress testing in women. Men appear to derive similar prognostic value from both types of tests.⁶⁶

Invasive testing

Some studies have shown sex-based differences in the use of coronary angiography, which may reflect physicians' failure to refer women with positive exercise stress test results,⁶⁷ leading to poorer patient outcomes. In one study, women with a positive exercise stress test result were more likely than men to have no further cardiac evaluation (62% vs 38%). At three years, this difference was associated with a higher incidence of acute myocardial infarction or death in non-revascularised women (14.3% vs 6% per year in men).⁶⁸ Other studies, however, have shown similar rates of coronary angiography following acute myocardial infarction.⁶⁹

Cardiovascular disease treatment

The management of cardiovascular disease in women must take into account sex-specific factors including the size of coronary vessels, bleeding risk and hormonal status, as well as potential pharmacokinetic and pharmacodynamic differences.

Revascularisation

Compared to men, women are nearly as likely to undergo percutaneous coronary angioplasty but less likely to undergo coronary artery bypass grafting.⁷⁰ It is unclear whether this represents bias or appropriate treatment given the higher mortality in women following coronary artery bypass grafting linked to increased comorbidities including smaller coronary vessels.

Cardiovascular pharmacotherapy

In younger women, dual antiplatelet therapy results in an increased risk of heavy menstrual bleeding and anaemia and needs close monitoring. Discussions about contraception use are important, as statins and ACE inhibitors are contraindicated in pregnancy. Prescribing may differ in women based on their reproductive age, other hormonal treatments and use of contraceptives.

Women with cardiovascular disease are more likely to receive nitrates, calcium channel blockers and sedatives and less likely to receive aspirin and statins than men,⁷¹ likely reflecting the higher prevalence of non-atherosclerotic cardiovascular disease. Statin use after acute myocardial infarction is also significantly lower in women than in men. This is partly physician driven and may be appropriate when myocardial infarction is due to MINOCA, which is more commonly encountered in women. However, low statin use in women with MI-CAD may be related to a reduced awareness among physicians of the risks of recurrent heart disease in women and a reduced likelihood to

consider heart disease as the main threat to women's health. Even women themselves often view cancer as a greater health threat. This may explain why women less often fill scripts for statins after myocardial infarction compared to men.⁷² To date, there is no evidence to support that statins are safer in men than in women. A large meta-analysis suggested that statin use to prevent major cardiovascular events has similar effectiveness in women and men,⁷³ and thus a poorer outcome in women is likely due to current practice.

Conclusion

Current guidelines for the diagnosis, investigation and treatment of cardiovascular disease do not discriminate between the sexes and are derived from male-dominant studies. Women remain more likely to experience delays in diagnosis and are less likely to receive guideline-directed care.

Attention to the differing contributions of traditional risk factors such as the presence of diabetes, physicians' compliance with established guidelines for the management of hyperlipidaemia, and a focus on lifestyle factors are fundamental to reducing the risk of cardiovascular disease in women. In addition, recognising the importance of sex-specific risk factors, such as hypertensive and metabolic disorders of pregnancy, are vital to improving outcomes.

While sex-specific cardiovascular research has increased significantly in recent years, this has not translated into changes in guideline-recommended care, nor has it improved clinical outcomes for women. Fundamentally, cardiovascular disease in women remains understudied, underdiagnosed and undertreated. Until this is addressed, women will continue to experience disproportionately high cardiovascular morbidity and mortality. ◀

Conflicts of interest: none declared

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