Does gender make a difference when managing cardiovascular disease?

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Over recent years, there have been significant improvements in the understanding of the role of gender in the pathophysiology, clinical manifestations and optimal treatment of cardiovascular disease (CVD). Despite this, disparities remain in the prevention, investigation and management of CVD in women.

CVD: the leading cause of death among women

In Australia, CVD is the leading cause of death among women, followed by dementia and stroke. The death rate from CVD increases greatly with age, peaking among women aged 85 years. Women generally present with CVD later than men and are more likely to die with CVD, either as a primary presentation or in combination with comorbidities. One in every five women is estimated to have CVD in the Australian population. Much of the CVD burden is attributable to modifiable risk factors; the presence of any cardiovascular risk factor increases the lifetime risk of ischaemic heart disease (IHD). More than 90% of Australian women have at least one modifiable risk factor for CVD and 50% of all women have two or three.[1]

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Key points

- Cardiovascular disease (CVD) is the leading cause of death among women. Compared with men, women generally present later and are more likely to die with CVD, either as a primary presentation or in combination with comorbidities.
- Certain traditional risk factors for CVD such as diabetes, dyslipidaemia and hypertension have both a higher prevalence and exert greater overall risk in women than men.
- Adverse coronary reactivity, microvascular dysfunction and plaque erosion/distal embolisation have been implicated as being significant contributors to the female-specific pathophysiology of myocardial ischaemia.
- Although women with acute coronary syndrome (ACS) do present with typical symptoms such as chest pain, they are more likely than men to present with atypical symptoms and with non-ST elevation ACS rather than ST elevation myocardial infarction.
- Compared with men, women often receive less intensive risk factor management before a coronary event and less intensive medical therapy, lifestyle counselling and cardiac rehabilitation after the event.
- Despite the distinct differences in both the pathophysiology and presentation of CVD in women and men, no discrepancies should exist in active detection and management of CVD. Further trial evidence is essential to determine the most appropriate CVD treatment based on gender.

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Women experience both increased mortality rates and poorer outcomes after a myocardial infarction than men. The 'Yentl syndrome', first described by Dr Bernadine Healy in *The New England Journal of Medicine* in 1991, highlighted the distinct sex bias in assessment and management of coronary disease, with women being significantly less likely to undergo coronary angiography, percutaneous angioplasty or coronary surgery when admitted to hospital with ACS.[2] Although significant improvements in awareness, investigation and management of CVD in women have been made since, disparities remain.

Influence of gender on CVD risk factors

Certain traditional risk factors for CVD such as diabetes, dyslipidaemia and hypertension have a higher prevalence and exert greater overall risk in women than men.

Women with diabetes are three to seven times more likely to develop or die of CVD than women without diabetes, compared with a two- to threefold increased risk in men.[3] Furthermore, women with diabetes have a worsened short-term prognosis following an acute coronary syndrome (ACS), with a higher risk of death, reinfarction and heart failure than men.[3]

Low-density lipoprotein (LDL) cholesterol concentration is lower and high-density lipoprotein (HDL) cholesterol concentration higher in premenopausal women than in men; after the menopause there is a significant increase in LDL- and decrease in HDL-cholesterol concentrations. Total cholesterol levels are higher on average in women than in men from the fifth decade of life.[4] A low HDL-cholesterol and higher triglyceride concentration is a more potent risk factor for CVD in women than men, and some data have suggested that an increased HDL-cholesterol concentration provides greater protective benefits in women than in men.[3]

Hypertension is particularly common in women. Gender-specific factors for this include their shorter stature and arterial trees, which result in faster resting pulse rates and lower diastolic blood pressure (BP).[5] Furthermore, following menopause, women experience a steep age-related increase in arterial wall stiffening. This is due to the loss of oestrogen influence on the vasculature via an effect on sympathetic nervous system activity and nitric oxide production.[6]

In addition to the significant prevalence of traditional CVD risk factors observed in women, factors unique to the female gender also predispose to CVD risk. Ovulation dysfunction is associated with increased risk of IHD and adverse CVD events.[7] Polycystic ovary syndrome (PCOS) is strongly associated with the presence of the metabolic syndrome and diabetes and subsequently an increased risk of IHD.[7] A history of pre-eclampsia in previous pregnancies doubles the risk for IHD in later life.[8]

Influence of gender on pathophysiology

One of the explanations for altered patterns of presentation between genders is that although underlying atherosclerotic processes are the same in men and women, women are significantly protected from these processes by oestrogen before menopause, which increases endothelial stretch and also provides both anti-inflammatory and antioxidative protection. Furthermore, oestrogen reduces cellular hypertrophy.[9]

According to ACS registries, at the time of diagnostic coronary angiography, women are more likely to have nonobstructive coronary artery disease (CAD) than men (10 to 25% *vs* 6 to 10%)[7] and are more likely to demonstrate myocardial ischaemia independent of coronary stenosis. In addition, women have relatively more preserved left ventricular systolic function despite having higher rates of myocardial ischaemia and mortality than men.[10] Findings from the Women's Ischemia Syndrome Evaluation (WISE) study have implicated adverse coronary reactivity,[11] microvascular dysfunction and plaque erosion/distal embolisation[12] as being significant contributors to the female-specific pathophysiology of myocardial ischaemia. From the WISE data, women presenting with symptoms and no obstructive CAD have a higher mortality and greater risk of adverse cardiovascular events compared with asymptomatic women, suggesting that despite the absence of obstructive CAD, the prognosis of women with signs of myocardial ischaemia is not benign.[13]

Microvascular coronary dysfunction (MCD) can be responsible for CVD events in women. Gender-based differences including smaller arterial size and more prominent positive remodelling may result in more MCD in women than men. Furthermore, endothelial response is adversely affected by traditional cardiac risk factors and also worsens after menopause, thus contributing to significant augmentation of endothelial dysfunction in older women.[13] Previous trials in which coronary artery reactivity testing and intravascular ultrasound were performed in men and women have shown less obstructive CAD and more MCD in women than men.[14] MCD and endothelial dysfunction predict adverse cardiovascular events[15] and have a significant role in IHD among women without obstructive CAD. Therefore further assessment of coronary reactivity in this patient cohort has been suggested.[16]

Pattern of acute coronary syndrome presentation

The presentation of ACS also varies between genders. Although women do present with typical symptoms such as chest pain, they are more likely to present with atypical symptoms than men and also more likely to present with non-ST elevation ACS rather than ST elevation myocardial infarction (STEMI).[17] It has also been noted that women are more often treated for psychosomatic illness rather than CVD,[18] which is potentially a reflection of a misconception that men are more likely to present with ACS than women and lack of knowledge that atypical symptoms occur more often in women.

The Framingham risk score has been used for many years as a tool to predict risk of IHD. This scoring system relies on traditional cardiac risk factors to predict risk and hence often underestimates risk in women.[19] Several novel risk markers have been suggested to aid in improving detection and optimising risk assessment in women such as high-sensitivity C-reactive protein (hs-CRP), which from puberty is

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consistently higher in women than men.[20] Elevations in hs-CRP levels are associated with greater risk of IHD than that predicted by traditional risk factors alone.[7]

Apical ballooning syndrome (Takotsubo cardiomyopathy) is often clinically indistinguishable on presentation from ACS and is much more common in women, predominantly of older age (Figure). Postulated mechanisms include catecholamine excess, coronary artery spasm and MCD, although it is not known why this disorder affects postmenopausal women disproportionately.[21]

Another uncommon but increasingly recognised aetiology of ACS with a striking predilection for the female gender is spontaneous coronary artery dissection (SCAD). More than 70% of SCAD cases are in women, and usually in those less than 50 years of age. Although the pathophysiology is not yet entirely understood, SCAD has been shown to be associated with minor atherosclerotic plaque rupture or, rarely, underlying connective tissue diseases such as Marfan's and Ehlers-Danlos type IV syndromes. Furthermore, one third of SCAD cases occur in the peripartum period, with a peak incidence in the second week after delivery.[22]

Role of gender in diagnostic approach

The role of gender in the approach to diagnosis of myocardial ischaemia has also been evaluated. Exercise stress testing is a commonly used approach; however, the sensitivity and specificity of ST-segment depression is lower in women than men, although this observation is somewhat influenced by the lower prevalence of obstructive CAD.[23] An exercise capacity of less than 5 METS or the inability to achieve greater than 85% maximum predicted heart rate has been shown to be a predictor of IHD-related and all-cause mortality in women.[7]

Single photon emission computed tomography (SPECT) imaging has been shown to be effective in risk stratifying women with suspected IHD. However, it does have some particular limitations in women, including reduced sensitivity due to diffuse endothelial/microvascular disease and breast attenuation.[24]

There is a dichotomy in the assessment of myocardial ischaemia. In assessing the accuracy of stress imaging it must be remembered that these tests provide a 'functional' assessment of the myocardium, whereas the gold standard of coronary angiography provides an 'anatomical' assessment of the coronary artery. In women with objective symptoms of ischaemia and resultant perfusion abnormalities in the absence of obstructive coronary disease, a functional test result can be inappropriately labelled as false positive.[25]

The outcomes of women presenting with CVD are further detrimentally affected by the co-existence of depression and anxiety. Depression and anxiety directly predispose patients to myocardial infarction and increase mortality both at the time of the event and in the first year after.[18]

Optimising therapy

Despite the differences in pathophysiology and presentation of CVD between women and men, both should receive optimal medical therapy. However, compared with men, women with CVD often receive less intensive medical therapy, lifestyle counselling and cardiac rehabilitation, which influence outcomes,[26,27] as well as having received less intensive risk factor management before the coronary event. This situation is occurring despite strong evidence that the management of CAD with intensive medical therapy benefits both genders equally.

The optimal treatment for symptomatic women with myocardial ischaemia and no obstructive coronary disease is yet to be determined; however, several drug classes, including beta blockers, statins and ACE inhibitors, have been shown to have either physiological or symptomatic benefit in this patient cohort.[7] Calcium channel blockers have been shown to be ineffective in this cohort.[28] In addition, exercise training in this female cohort has been shown to improve symptoms.[7]

Conclusion

CVD contributes greatly to the health burden across both genders and continues to be the leading cause of death among women. Following the identification of a significant discrepancy in the assessment and management of women with CVD compared with men, the awareness of women's cardiovascular risk both in the medical and wider communities has improved, but further education is needed for both. Furthermore, the different pathophysiology of myocardial ischaemia beyond typical obstructive coronary disease in women contributes significantly to their increased risk of adverse cardiovascular events. Appreciation of this is essential in the assessment and investigation of CVD in women.

Despite the distinct differences in both the pathophysiology and presentation of CVD in women and men, no discrepancies should exist in active detection and management of CVD. Further trial evidence is essential, however, to determine the most appropriate CVD treatment based on gender. **CT**

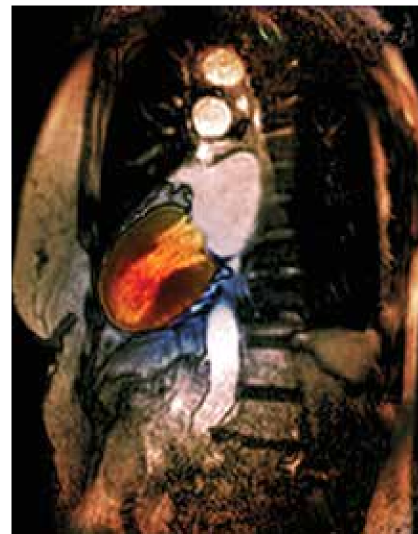

Figure. MRI of the heart (left anterior oblique view after contrast injection) showing Takotsubo cardiomyopathy with transient ballooning of the left ventricle in a 77-year-old woman.

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A list of references is included in the website version of this article (www.cardiologytoday.com.au).

COMPETING INTERESTS. None.

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