

Acute coronary syndromes in women

Different presentation and poorer outcomes

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Despite being more likely to present with NSTEMI than STEMI, women have worse outcomes after an ACS than men, due in part to older age at ACS occurrence and having more comorbidities. Women generally have longer delays from symptom onset to treatment and are more likely not to report chest pain and less likely to have diagnostic ECG changes and elevated troponin levels.

Although women have a lower incidence of acute coronary syndromes (ACS; including ST segment elevation or non-ST segment elevation myocardial infarction [STEMI and non-STEMI, respectively] and unstable angina) compared with men, coronary heart disease remains the leading cause of mortality regardless of gender. Women experiencing a heart attack are more likely to delay presentation to medical care, are less likely to report typical chest pain and are more likely to report a wider range of symptoms, including dyspnoea and nausea. These factors may delay appropriate diagnosis and early delivery

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of effective treatments. Women usually present at a later age and have higher rates of comorbidity, which translates to a worse prognosis post-ACS than men.

This article explores the differing patterns of presentation, treatment patterns and prognosis in women with ACS. The difficult but important role of the GP is to be aware of the variable presentations of heart attacks in women so they can be distinguished from the more common and less serious causes of chest pain and dyspnoea encountered, and to reduce barriers to prompt treatment and ensure that women receive the same effective postcoronary event management as men.

Hospitalisations for ACS

With respect to incidence of coronary events, men have consistently higher rates of hospital admission for acute coronary events than



KEY POINTS

- The widespread community perception that heart attack is a 'man's disease' may contribute to longer delays in women presenting with suspected acute coronary syndrome (ACS).
- Heart attacks are common in older women and urgent hospital transfer for effective management is vital.
- Presentation of ACS in women can be atypical with dyspnoea, nausea and fatigue, rather than typical angina pain. Being alert to these atypical presentations avoids delays in treatment.
- Takotsubo cardiomyopathy is far more common in women than in men. It is brought on by sudden emotional stress and usually resolves with a favourable prognosis.
- Women have a worse prognosis after an ACS. It is not clear if this is due to later age at presentation, undertreatment or sex differences.
- Women respond just as well as men to early reperfusion therapies for coronary occlusion, but if there are delays in diagnosis or treatment delivery, their outcome is worse.
- Women receive less invasive treatments than men when they have an ACS. This may be appropriate because of older age and more comorbidities but this valuable form of treatment should not be denied because of diagnosis delays or gender bias.

Pattern of presentation of ACS

The pattern of coronary disease and ACS presentation appears to differ in men and women.^{5,6} Women have less obstructive coronary artery disease and a higher prevalence of microvascular coronary dysfunction.⁷ Although most women presenting with an ACS experience typical anginal symptoms, more women than men do not report chest pain or pressure. Women are, however, more likely than men to report associated symptoms, including dyspnoea, nausea and fatigue.⁸ The higher average age of women at ACS presentation may partly explain these differences, with older patients of both sexes less likely to report chest pain. Women also have a higher rate of comorbidities such as diabetes, hypertension and prior heart failure than men, and fewer present with STEMI.^{9,10} The significance of these differences is being examined in a large international cohort of younger patients presenting with ACS.¹¹

There is a higher prevalence of Takotsubo cardiomyopathy (also known as stress cardiomyopathy) among women than men, with women comprising 90% of patients presenting with this condition.¹² This unusual form of ACS usually occurs with acute emotional stress and is frequently accompanied by ECG ST-segment elevation and a rise in troponin levels. There is characteristic but most commonly transient dysfunction of the left ventricle and near normal coronary arteries.¹³ The reasons for the marked

women across all age groups, but the relative difference in rates by sex decreases substantially in the older ages, from around twice as high in those aged less than 75 years to around 1.3 times higher in those aged 85 years and over (Figure 1).¹ When all age groups are considered, women account for just under half of all patients who are hospitalised with ACS, up to 45% in some series and 40% in a comprehensive snapshot of admissions to coronary care units in Australia and New Zealand in 2012.^{2,3}

Trends in ACS

There has been an encouraging downward trend in age-standardised rates of fatal coronary heart disease over the past 30 years. The decline in the rates over the five years from 2007 to 2012 was similar for women and men, 26% and 23%, respectively (Figure 2).^{1,4}

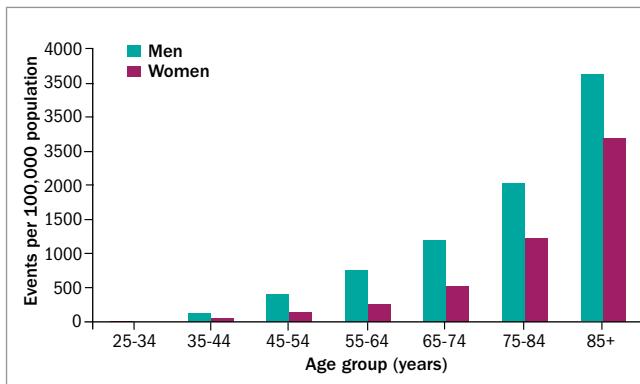


Figure 1. Acute coronary event rates, men versus women by age. There is a marked preponderance of males versus females in younger age groups, but less so in older age groups.

Source: Australian Institute of Health and Welfare.¹

gender variation are poorly understood.¹⁴

Sex differences in the reference range and pattern of troponin level elevation may complicate the diagnosis of ACS when the myocardial damage is minimal.¹⁵ Although the diagnostic and prognostic performance of troponin levels is similar in men and women, the use of sex-specific cut-off levels have been shown to be clinically significant in predicting prognosis.^{16,17}

Women are more likely to present with non-ST elevation ACS than men.^{18,19} The difference in ECG pattern is largely explained by the older age and associated comorbidities of women presenting with ACS.

Delays in time to presentation after an ACS event are consistently longer in women than in men.²⁰ The delays in women are influenced by older age, living alone, being alone during symptom onset, and the patient not wanting to bother anyone. These differences in response time impact on time to reperfusion for patients with STEMI.²¹

Outcomes after ACS

Women have worse short- and long-term outcomes after an ACS than men.²² The most likely explanation for this is that women suffer a heart attack about a decade later in age than men, but the precise reason for this large gender difference remains

controversial and may reflect other factors such as different comorbidities, time to presentation and management.²³

After detailed multivariate analysis of age and other prognostic factors, female gender is an independent predictor of outcome for STEMI but not for non-ST elevation ACS.²⁴ The disparity in outcomes for STEMI is particularly evident in younger women who have a higher risk of death and recurrent events compared with similarly aged men. In a Swedish registry of approximately 350,000 patients, in which women aged less than 50 years had higher mortality rates than men at 28 days and one year, the excess was largely attributable to a higher prevalence of diabetes.²⁵ Among the approximately 385,000 patients from the US National Registry of Myocardial Infarction (NRMI), the odds of death in women with STEMI were 7.0% higher (95% confidence interval, 5.9–8.1%) than in men for every five years of decreasing age even after adjustment for medical history, clinical severity and early management.²⁶ Similar findings were seen in a study of 12,000 patients in China.²⁷

These differences have been recognised for decades, and remain even in the modern era of early intervention; careful analyses with detailed adjustment have shown that the differences are most likely due to age and higher baseline risk.^{28,29} An interesting recent publication attempted to separate

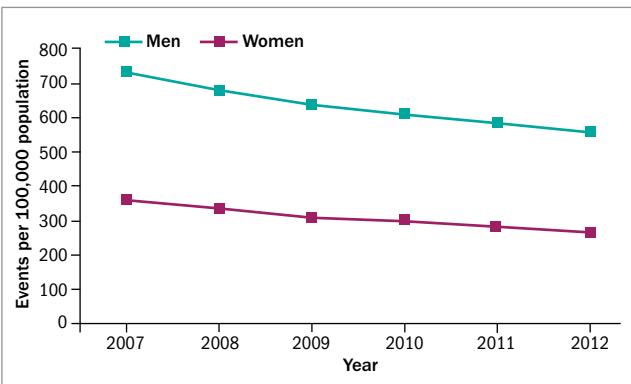


Figure 2. Trends in acute coronary event rates, men versus women. Downward trends in incidence of acute coronary events are seen equally in men and women.

Source: Australian Institute of Health and Welfare.¹

the influences of female sex from feminine gender characteristics, suggesting that the latter were a more important predictor of outcome than female sex.³⁰

Do women respond differently to early invasive treatment?

Some studies have suggested that women experiencing an ACS may not receive the same benefit from invasive management as men.³¹

The trials comparing conservative with invasive management were under-powered to demonstrate a benefit in women, and reports from meta-analyses of the trials have yielded conflicting results. Trials to 2008 showed a clear benefit of invasive management in women at higher risk, but a more recent meta-analysis including the data from the OASIS 5 trial (Organization to Assess Strategies in Acute Ischemic Syndromes Investigators) failed to demonstrate any benefit for women from an early invasive approach.^{32,33}

Differences in comorbidities may explain the observed response to intervention in STEMI.³⁴

There is also evidence that women have a higher bleeding and adverse event risk with the potent antithrombotic agents that accompany percutaneous intervention, possibly because of relatively excessive dosing.³⁵

Are women being undertreated when they have an ACS?

Women with ACS receive invasive management less frequently than men. The difference is probably because of higher rates of comorbidity rather than a treatment bias, but difficulties in diagnosis may also contribute.³⁶ In a recent large US series of young patients, there was less use of timely reperfusion therapies in women than in men, and careful adjustment indicated a likely sex difference.³⁷ An Australian study showed lower use of intervention in women than men, although there was incomplete adjustment for other factors in that study.³⁸ Despite these reports, there is no convincing evidence that the worse outcome for women is solely because of a lower rate of intervention.³⁹ The trends to improved treatments as a result of clinical trial evidence have been seen equally in women and men.⁴⁰

After recovery from ACS, women are less likely to receive guideline-indicated pharmacotherapies. The evidence for undertreatment with appropriate anti-thrombotic therapy in women is particularly strong. Lower body weight and estimated glomerular filtration rates, especially among older women, indicate the need for caution to avoid excess dosing of antithrombotic therapy.⁴¹ However, analyses of the use of antiplatelet therapies after ACS showed no differences in ischaemic or bleeding outcomes for the newer agents prasugrel and ticagrelor.^{42,43}

The clinical trial evidence base for treatment after an ACS episode includes far fewer women than men.⁴⁴ Despite this, there is no clear evidence that the usual post-ACS medications are less efficacious in women than in men. Equivalent efficacy for women and men has been shown for the use of aspirin, clopidogrel and ticagrelor post-ACS, as well as the short- and long-term use of β-blockers, statin therapy and ACE inhibitors after myocardial infarction.⁴⁵⁻⁵⁰ Clinical trials of hormone replacement therapy have shown no benefit, but also no adverse effect, after ACS.⁵¹

Conclusion

In Australia, approximately 20 women suffer a heart attack each day. GPs should be aware that women may delay presentation and report a wider range of symptoms when experiencing an ACS, which may lead to avoidable delays and undertreatment. The prognosis of women with ACS is worse than that of men and controversy over whether this is due to later age at presentation, more comorbidities, gender differences or undertreatment remains unresolved.

Early diagnosis is essential and prompt management is effective at reducing mortality and improving outcomes post-ACS. Women respond just as well as men to acute in-hospital treatments and post-hospital secondary prevention. The GP plays a key role in ensuring that long-term adherence to evidence-based treatment regimens post-ACS is as much a priority for women as for men.

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

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