

## **Cardiovascular disease in women: implications for improving health outcomes**

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## **Abstract**

**Objective:** To collate data on women and cardiovascular disease in Australia and globally to inform public health campaigns and health care interventions.

**Design:** Literature review

### **Results:**

- Women with acute coronary syndromes show consistently poorer outcomes than men, independent of comorbidity and management, despite less anatomical obstruction of coronary arteries and relatively preserved left ventricular function. Higher mortality and complication rates are best documented among younger women and those with ST-segment-elevation myocardial infarction.
- Sex differences in atherogenesis and cardiovascular adaptation have been hypothesised, but not proven.
- Atrial fibrillation carries a relatively greater risk of stroke in women than in men, and anticoagulation therapy is associated with higher risk of bleeding complications.
- The degree of risk conferred by single cardiovascular risk factors and combinations of risk factors may differ between the sexes, and marked postmenopausal changes are seen in some risk factors.
- Sociocultural factors, delays in seeking care and differences in self-management behaviours may contribute to poorer outcomes in women.
- Differences in clinical management for women, including higher rates of misdiagnosis and less aggressive treatment, have been reported, but there is a lack of evidence to determine their effects on outcomes, especially in angina.
- Although enrolment of women in randomised clinical trials has increased since the 1970s, women remain underrepresented in cardiovascular clinical trials.

**Conclusions:** Improvement in the prevention and management of CVD in women will require a deeper understanding of women's needs by the community, health care professionals, researchers and government.

## **Introduction**

### **Background**

Cardiovascular disease (CVD) is the leading cause of death and disability in Australian women (Australian Bureau of Statistics, 2009; Australian Institute of Health and Welfare, 2004, 2008). Coronary heart disease (CHD) ranks first among causes of death in Australian women (17.5% of deaths), followed by cerebrovascular disease (10.8%) (Australian Bureau of Statistics, 2009; Australian Institute of Health and Welfare, 2008). In 2007, 61% of Australians who died from stroke, 60% of those who died from heart failure and 47% of those who died from CHD were women (Australian Bureau of Statistics, 2009). The 2004–2005 Australian Bureau of Statistics National Health Survey found a higher CVD prevalence in women (55%) than men (45%) (Australian Institute of Health and Welfare, 2008). After adjusting for women's relative longevity, about one in five Australian women has CVD, compared with about one in six men (Australian Institute of Health and Welfare, 2008).

Despite these statistics, most Australian women are unaware that heart disease is a major women's health issue, (Guillemin, 2004)<sup>1</sup> and even those who have experienced an acute myocardial infarction (AMI) often fail to recognise their lifestyle risk factors (Worrall-Carter, et al., 2005) (Murphy et al., 2005). The Heart Foundation's *Go Red For Women* campaign is raising awareness of CVD in women aged 40–65 years among the community, health professionals and researchers. These efforts are part of a long-term strategic program that aims to reduce CVD in women by promoting healthier lifestyles through smoking cessation, healthy eating and regular physical activity.

### **Method**

We searched electronic databases (Cumulative Index of Nursing and Allied Health Literature, Medline, Embase, Science Direct and Scopus) using the following keywords: women, female, diagnostic techniques, cardiovascular disease, coronary heart disease, angioplasty, transluminal, percutaneous coronary, coronary artery

bypass, and myocardial revascularisation. We also conducted a web-based search using Google Scholar search engine and other strategies, and hand-searched articles and reports. We considered data from published peer-reviewed articles, unpublished and informally published literature.

## **Findings**

### **Part A. Is women's cardiovascular disease different?**

#### Coronary heart disease

##### *Prevalence and disease burden*

Almost one in four (18%) Australian women has CHD, compared with 30% of men (Australian Bureau of Statistics, 2006). Although the age-standardised prevalence of CHD is lower for women than men by about one-third, (Australian Institute of Health and Welfare, 2004) women's longer life expectancy results in a higher prevalence for women in the over-75 age group (Australian Institute of Health and Welfare, 2004). Coronary heart disease is the second highest contributor to disease burden (as measured by disability-adjusted life years) amongst Australian women, after anxiety and depression (Begg, Vos, Barker, Stanley, & Lopez, 2008). The prevalence and costs of CHD in Australian women are likely to increase in the near future (Access Economics, 2005).

##### *Outcomes*

In large United States (US) studies, women with acute coronary syndromes (ACS) have shown consistently poorer short-term and long-term outcomes than men, independent of comorbidity and management (Ng, 2007) (Roger et al., 2011). Compared with age-matched men, women with CHD experience higher rates of acute myocardial infarction (AMI) and show higher rates of death due to CHD, despite apparently less anatomical obstruction of coronary arteries and relatively preserved left ventricular function (Shaw, Bugiardini, & Merz, 2009; Vaccarino, 2010).

Studies among US women also suggest that they have a poorer prognosis than men after a first AMI (American Heart Association, 2008; Vaccarino, 2010). Among those aged 40 years and older, 23% women die within one year, compared with 23% of men. Approximately 35% of women who survive an AMI will have another within 6

years, compared with 18% of men, and 46% of women will be disabled with chronic heart failure (CHF) within 6 years, compared with only 22% of men. Women are almost twice as likely as men to die following cardiac bypass surgery (American Heart Association, 2008). These differences underscore the importance of targeted initiatives focussing on the specific needs of women (Mosca et al., 2011).

Women's poorer prognosis for CHD is partly due to older age at onset and associated higher rates of comorbidity. However, North American studies have reported higher mortality and morbidity rates in women post AMI after controlling for age, disease severity and comorbidity, (Vaccarino, 2010) and higher rates of fatal and nonfatal complications after thrombolytic therapy for AMI after adjusting for differences in age and presentation (Weaver et al., 1996). Women with CHD also report worse health-related quality of life than men (Norris et al., 2004). Sociodemographic factors may contribute to this increased disease burden.

Overall, higher mortality and complication rates for ACS in women compared with men have been demonstrated mainly in two groups of women: the young to middle-aged, and those with ST-segment-elevation MI (Vaccarino, 2010). The reasons for relatively higher risk in these groups are remain unknown (Vaccarino, 2010).

#### *Presentation and symptoms*

Women with CHD are more likely than men to present with unstable angina (Lerner & Kannel, 1986) or with non-ST-segment elevation ACS (Pilote et al., 2007).

Although chest pain is the most common symptom of AMI in both sexes, atypical symptoms such as nausea and jaw pain may occur more often in women (Canto et al., 2007; Kennedy et al., 1982; Milner et al., 1999). Women with CHD may perceive angina differently from men, and experience more chest pain during normal daily activities (Sheps et al., 2001).

Although women with CHD have more symptoms and physical limitations than men, studies in women with ACS or referred for revascularisation have reported less coronary artery obstruction (Vaccarino, 2010). Current evidence suggests that women are more likely than men to experience a syndrome of chest pain in the absence of

obstructive coronary artery disease, and that chest pain in women does not correlate with severity of stenosis (Vaccarino, 2010).

Some investigators have hypothesised that these findings might be explained by sex differences in the pathophysiology of CHD, such as differences in intravascular remodelling in response to atherosclerotic plaque build-up, differences in patterns of plaque deposition, vasoconstriction due to coronary endothelial dysfunction, coronary microvascular disease, and global inflammation (Bailey Merz et al., 2006; Blum & Blum, 2009; Shaw, et al., 2009; Vaccarino, 2010). Accordingly, standard perfusion studies to detect coronary artery stenosis might be less accurate in determining true cardiovascular risk in women (Bailey Merz, et al., 2006; Matyal, 2008). However, the presence of vascular abnormalities in the absence of coronary artery obstruction has not been clearly demonstrated to be a more common cause of ischaemia in women than in men (Vaccarino, 2010).

### Heart failure

#### *Prevalence and disease burden*

There are no reliable prevalence statistics for chronic heart failure (CHF) in Australia. Based on 2004–2005 National Health Survey self-reports, approximately 1% of Australian women have CHF (Australian Institute of Health and Welfare, 2008).

#### *Outcomes*

Australian women are approximately 28% less likely than men to be hospitalised for heart failure (Australian Institute of Health and Welfare, 2004). However, heart failure is the principle cause of death for more women than men because women live longer (Australian Institute of Health and Welfare, 2008) (Teng et al., 2011).

North American data show that overall, the probability of dying within 5 years of the diagnosis of CHF is approximately 50% for women and for men, (Pilote, et al., 2007) and overall survival times after a diagnosis of CHF are slightly longer for women than men (Pilote, et al., 2007). However, the strong decline in heart failure death rates seen in men over the past 20 years have not been matched in women, ( Roger et al., 2004) and the prevalence of clinically significant CHF among women is increasing (Pilote, et al., 2007). North American rates of hospitalisation due to heart failure has

increased more sharply in women than in men (Pilote, et al., 2007). Teng and colleagues have demonstrated the increased burden of hospitalisation for heart failure of non-ischaemic aetiology (Teng, et al., 2011).

### Atrial fibrillation

#### *Prevalence and disease burden*

There are no reliable prevalence data for atrial fibrillation (AF) in Australia. North American data suggest that the age-adjusted prevalence of AF is lower in women than men, but the absolute numbers of men and women with AF are approximately equal because women over 75 years outnumber men (Pilote, et al., 2007).

#### *Outcomes*

Studies published during the past 20 years suggest that women with AF are more likely than men to experience symptomatic attacks, have a higher frequency of recurrences, and show significantly higher heart rates than men during AF (Volgman, et al., 2009), AF also appears to confer a relatively greater risk of stroke in women than in men (Pilote, et al., 2007).

Women may have a higher risk of bleeding due to anticoagulation therapy for AF, (Pilote, et al., 2007) and in premenopausal women the effect of the menstrual cycle on QT intervals must be considered when selecting antiarrhythmic agents (Volgman, et al., 2009).

### Stroke

#### *Prevalence and disease burden*

While the age-standardised death rate due to stroke is slightly lower among Australian women than men, the absolute number of deaths due to stroke is approximately 50% higher in women because over 80% of deaths occur in Australians over 75 years (Australian Institute of Health and Welfare, 2008). Age-standardised death rates for stroke are declining approximately equally in men and women (Australian Institute of Health and Welfare, 2008). It has been predicted that by 2050, mortality from stroke will be 30% higher in women than men (Kurth & Bousser, 2009).

### *Outcomes*

North American and Scottish data show that women with a history of stroke have higher hospital readmission rates than men (Pilote, et al., 2007) (Lewsey et al., 2010).

### Peripheral arterial disease

#### *Prevalence and disease burden*

There are currently no data on the prevalence of peripheral arterial disease (PAD) in women in Australia. International studies indicate that the prevalence of PAD amongst women ranges from 5.5% to 29% (Wilbert S. Aronow, 2009; Vavra & Kibbe, 2009), increasing with age. Evidence suggests that women may be less likely to experience typical claudication symptoms which may lead to less recognition of PAD in women. However, compared to men, it has been demonstrated that women with PAD have faster functional decline and experience greater mobility loss (McDermott et al., 2011).

### *Outcomes*

Women with PAD are at significant risk of all-cause and cardiovascular mortality and cardiovascular events such as stroke and AMI (Aronow, Ahmed, Ekundayo, Allman, & Ahmed, 2009).. Dutch data indicate that following an initial hospitalisation for PAD, 10.4% of women were dead after 1 year and 27.4% at five years; 61.9% of deaths in women at 1 year and 53.7% at 5 years were attributed to cardiovascular cause (Vaartjes et al., 2009). Lower intervention rates have been reported for women, compared to men (Egorova et al., 2010; Vouyouka et al., 2010).

## **Part B. What factors might explain CVD sex differences?**

### Physiological differences

Different coronary artery anatomy, hormonal effects on the cardiovascular system and body fat distribution may affect women's and men's CVD risk. It is well established that premenopausal women have a much lower incidence of CHD than age-matched men, and that the incidence of CHD among women increases rapidly after menopause (Pilote, et al., 2007) (Vaccarino et al, 2011). However, it remains unclear whether the influence of menopause on CHD is primarily related to changes in oestrogen levels, or to the other age-related risk factors such as hypertension (Gierach et al., 2006).

Endogenous oestrogen has been thought to confer CVD protection, but oestrogen



replacement therapy has not been shown to improve cardiovascular outcomes and is not recommended in the primary prevention of CVD in postmenopausal women (National Health and Medical Research Council, 2005).

### Cardiovascular risk factors in women

The major risk factors for CVD identified in mixed populations and in men also apply to women, and intensive risk-factor modification appears to be effective in countering plaque progression women as for men (Blum & Blum, 2009). Data from the international INTERHEART study suggest that 94% of population attributable risk in women (versus 90% in men) is accounted for by nine risk factors: smoking, raised ApoB/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, inadequate daily consumption of fruits and vegetables, abstinence from alcohol consumption (protective effect associated with regular use), and inadequate physical activity.

Overall, the prevalence of biomedical and lifestyle risk factors are generally similar in Australian women and men (Table 1), but marked postmenopausal changes are seen in some risk factors, such as lipid profile (Australian Institute of Health and Welfare, 2008), North American studies show that premenopausal women have lower blood pressure (BP), low-density-lipoprotein (LDL) cholesterol and lower plasminogen activator inhibitor type-1, and higher levels of high-density-lipoprotein (HDL) cholesterol than men, but that after menopause cardiovascular risk profiles are more similar to those of men ( Evangelista & McLaughlin, 2009; Pilote, et al., 2007).

Women experience higher rates of potential psychosocial risk factors such as depression, stress associated with family or work, socioeconomic deprivation, and adverse early life events (Vaccarino, 2010). However, the role of psychosocial risk factors in CVD among women has not been well evaluated (Vaccarino, 2010) (Low, Thurston, & Matthews, 2010).

The degree of risk conferred by individual risk factors and combinations of risk factors may differ between the sexes (Table 2). The risk of CVD has been reported to increase more steeply in women than in men with each additional risk factor (Oda et al., 2006).

### Evidence bias

The prevention and management of heart disease in women is largely based on strategies developed and tested in men and it is not clear to what extent the findings apply to women (Ghali, 2009; Meagher, 2004). Although enrolment of women in randomised clinical trials has increased since the 1970s, women remain underrepresented cardiovascular clinical trials (Melloni et al., 2010). A recent analysis of clinical trials cited by the American Heart Association's 2007 guidelines for CVD prevention in women (Mosca et al., 2007) found that women comprised only 29% of patients in heart failure trials, 25% of those in CHD trials and 28% of those in hyperlipidaemia trials, and that sex-specific findings were reported in only 31% of original trial publications (Melloni, et al., 2010).

Male bias in trial sampling may mask differences between sexes in treatment responses. A recent meta-analysis concluded that implantable cardioverter-defibrillator therapy for the primary prevention of sudden cardiac death in women does not reduce all-cause mortality (Ghanbari et al., 2009) .

### **Part C. Which non-biological factors might affect women's CVD?**

#### Community knowledge and beliefs

Lack of recognition of women's cardiovascular risk may preclude effective prevention and management. A 2008 national survey of 1,964 Australian women aged 30–65 years commissioned by the Heart Foundation in found that:

- Only 22% were aware that heart disease is the leading cause of death in women.
- While 95% recognised smoking, poor diet and physical inactivity as CVD risk factors, almost two-thirds (65%) did not identify high BP, high cholesterol or diabetes as risk factors.
- More than 50% believed that heart disease was more common amongst men than women.
- There was limited awareness that the risk of heart disease in women increases with age, especially after menopause.

- A substantial number of women reported they were regularly screened for high BP, but were less likely to be assessed for cholesterol or diabetes (National Heart Foundation 2008).

A similar lack of awareness of CVD as a major women's health issue has been documented in US women (Ferris, Robertson, Fabunmi, Mosca, & American Heart Association, 2005; Mosca et al., 2006).

#### Gender-based differences in health behaviours

Delays in seeking care may contribute to poorer outcomes in women, which are not entirely explained by the relative older age and associated higher rates of comorbidity among the female CVD population. Several investigators have documented evidence that women may experience CVD differently from men (Daly et al., 2002; . Evangelista, Kawaga-Singer, & Dracup, 2001; Hammond, Salamonson, Davidson, Everett, & Andrew, 2007; Lefler, 2004; Nau et al., 2005; Rosenfeld, 2001).

Women are more likely to underestimate their CVD risk than men (Evangelista, et al., 2001; Hammond, et al., 2007; Lefler, 2004). Women with ACS have been reported to rate their cardiac disease as less severe than men, after controlling for other measures of cardiac disease severity (Nau, et al., 2005). Women are also significantly less likely to report chest pain or discomfort compared with men (Canto, et al., 2007). During ACS, women are more likely to delay seeking medical care than men, (Goldberg, Gurwitz, & Gore, 1999; O'Donnell, Condell, Begley, & Fitzgerald, 2006; Rosenfeld, 2001) for reasons that may include attributing symptoms to other causes, fear of bothering anyone, embarrassment about a 'false alarm' and reluctance to call emergency medical services (Dracup, 2007).

Women who have experienced an AMI may be less likely than men to adopt lifestyle changes including healthy eating and increasing physical activity, (DiGiacomo, Davidson, Zecchin, Lamb, & Daly, 2011; Martin et al., 2005) consistent with weaker attribution of their AMI to lifestyle risk factors (Martin, et al., 2005). Participation rates for coronary rehabilitation are lower in women than men (Daly, et al., 2002). An Australian study among patients eligible for a structured cardiac rehabilitation program after a cardiac event found that only 22% of women participated, compared

with 78% of men (Davidson et al., 2008). Older women experience special barriers to adopting exercise in the self-management of CVD, including a low self-rating of their ability to undertake physical activity and poor tolerance of physical activity (Lee, 1993; Moore, 1996).

#### Sex-based differences in health care

Misdiagnosis and less aggressive treatment in women have been commonly reported. In the Framingham Heart Study cohort, 50% of AMIs in women were unrecognised, compared with 33% in men (Murabito, 1995). Another US study reported that women presenting to the emergency department with AMI were more likely to be discharged without admission than men, and that those under 55 years were at highest risk of misdiagnosis (Pope et al., 2000).

Even after diagnosis, potentially clinically significant differences in treatment have been reported. A Canadian report found that, compared with men, women were less likely to be treated by a specialist, less likely to be transferred to another facility for treatment, and less likely to receive cardiac catheterisation or revascularisation (Spurgeon, 2007). It has been hypothesised that adverse outcomes of CHD in women compared with those in men might reflect the current focus of treatment on obstructive coronary artery disease, and that this model may not apply equally to women's CVD (Shaw, et al., 2009).

Most research investigating sex-based differences in clinical management of CVD has focussed on ACS – to the relative neglect of angina, the most common manifestation of CHD in women (Vaccarino, 2010) .

## **Discussion**

Differences in women's CVD risk, presentation, management and experience highlight the need for health professionals to develop chronic disease prevention and treatment strategies for women. The National Health and Medical Research Council's 2004 *Clinical practice guidelines for the management of overweight and obesity in adults* (National Health and Medical Research Council, 2004) is example of this approach, identifying separate strategies for weight loss that work best in women and

in men. A gender-specific approach to CVD management is gaining momentum internationally, as evidenced by the World Heart Foundation's Go Red For Women campaign, yet identifying the most important messages remain controversial (Canto, et al., 2007; Engberding & Wenger, 2008).

Cardiovascular disease is often overlooked as a women's health issue (Wenger, 2011). Australian women need reliable information about their risk for CVD and encouragement to engage in healthy behaviours and correct biomedical risk factors, respond promptly to symptoms such as heart attack warning signs, and obtain appropriate health care when needed. Messages should be tailored for women from high-risk groups, including those living outside metropolitan areas, (Sexton & Sexton, 2000) Aboriginal and Torres Strait Islander women, (Australian Institute of Health and Welfare, 2008) and those who are socioeconomically disadvantaged (Turrell, Stanley, de Looper, & Oldenburg, 2006).

The Heart Foundation's Go Red for Women Campaign draws on recent US experience demonstrating that women's knowledge of CVD and their risk can be substantially improved by public awareness campaigns (Mochari-Greenberger, Mills, Simpson, & Mosca, 2010). Cardiovascular disease prevention will be included in the Federal Government planned 10-year national women's health policy, (Australian Government, 2009) which will recognise gender as a basic determinant of health affecting health outcomes and health care needs.

## **Conclusions**

Improvement in the prevention and management of CVD in women will require a deeper understanding of women's needs by the Australian community, health care professionals, researchers and government.

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