Female gender and cardiovascular disease

Despite a generalized belief that women are protected from cardiovascular disease, this remains the leading cause of death in women. This review focuses on differences in symptomatology, diagnostic modalities and therapeutic strategies in women with regard to cardiovascular disease.

Traditionally, cardiovascular disease has been mostly considered to affect men and discussions of risk, symptoms and threats focus primarily on men. The female gender is often overlooked and is not well studied in many aspects of cardiovascular research. In fact, only 30% of cardiovascular clinical trials since 2006 enrolled women, and only 50% of these trials actually involved gender analysis (Prata et al, 2014). Thus results obtained from clinical trials involving mostly men are extrapolated to women, ignoring the possibility of there being any gender differences.

Far from being a problem restricted to men, cardiovascular disease is the leading killer in women. Globally, it is the greatest cause of death in women, accounting for one-third of all deaths and amounting to 8.6 million women each year. Myocardial infarction kills approximately four times as many women as breast cancer (Mozaffarian et al, 2015). Furthermore, cardiovascular disease kills a higher percentage of women than men: in 2004, cardiovascular disease was the cause of 32% of deaths in women as opposed to 27% in men worldwide (Vaccarino et al, 2010). While the mortality rate from coronary artery disease is declining in men, the opposite has been noted in women. The National Health and Nutrition Examination Surveys (NHANES) have found that the rate of myocardial infarction in middle-aged women (35–54 years) has increased over the past 20 years, while it has decreased over that time in men of the same age group.

Cardiovascular disease develops 7–10 years later in women than in men; nonetheless, women have higher mortality rates. Over the age of 45 years, 26% of women die compared to 19% of men (Mozaffarian et al, 2015). Women also have a higher incidence of development of heart failure following myocardial infarction (46% in women *vs* 22% in men). Nonetheless, the great threat which cardiac disease poses to women is still greatly underappreciated, as evidenced in surveys among American women where about 50% of women were aware that heart disease is the major killer of women, yet only 13% acknowledged that it was their greatest personal health risk. This review unravels the underlying differences in symptomatology between male and female sex as well as analysing available data with regard to the best available options for diagnosis and treatment of cardiovascular disease in women.

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Symptomatology

Women with coronary artery disease are more likely to present with atypical symptoms than men. These include abdominal pain, shortness of breath, back and neck pain, indigestion, nausea or vomiting, palpitations and fatigue (Prata et al, 2014). Even before ST-segment elevation myocardial infarction, women have a higher incidence of non-chest pain symptoms. These atypical symptoms may lead to misdiagnosis of the condition by the physician, such as attributing the symptomatology to gastrointestinal disease. The patient may also take longer to seek medical advice.

Left-sided chest pain with radiation to the left shoulder may also be the initial symptom although this occurs less commonly in women than in men. Furthermore, chest pain in women is less likely to be linked to the presence of coronary atherosclerosis. Women diagnosed with non-cardiac chest pain have double the chance of developing a cardiac problem in the next 5–7 years, and are four times more likely to be admitted back to hospital and undergo recurrent angiograms in the next 180 days. This could be explained by a high incidence of obstructive coronary

artery disease in women presenting with atypical chest pain (*Figure 1*). This has been evidenced in a study of 1148 patients whereby computed tomography coronary angiography revealed that diabetes mellitus, female gender and age were independent predictors of obstructive coronary artery disease in subjects presenting with atypical chest pain; this was independent of diabetes duration (Krul et al, 2014).

The presence of gender difference in myocardial ischaemic symptoms was demonstrated by Tamura et al (2013) where non-chest pain symptoms while 60-second balloon occlusion of the coronary artery was carried out during percutaneous coronary intervention were more common in women than in men. These non-chest pain symptoms included occipital pain, jaw pain, neck or throat pain, shoulder pain, upper arm pain, back pain and nausea.

The atypical symptomatology in women underlies the fact that the traditional diagnostic measures are not the best option for women. Risk factors should be addressed more rapidly and more effectively in women. Furthermore, a high index of suspicion should always be maintained and non-chest pain symptoms should be adequately and effectively investigated. This is especially important because prompt recognition of prodromal symptoms in women before an acute coronary syndrome results in higher rates of survival in women than men (Graham et al, 2008).

Diagnostic modalities

Interpretation of tests performed for the diagnosis of coronary artery disease is generally less reliable with higher false positive rates in women, especially those younger than 55 years of age. Various tests are used in the assessment of chest pain (*Figure 2*). The interpretation of electrocardiograms has no gender-specific criteria. However, women's resting heart rate is generally higher than that of their male counterparts, sinus node recovery time is shorter and heart rate variability is more pronounced, reflecting the higher parasympathetic influence in women. Interestingly, resting heart rate is an independent risk factor for all-cause mortality in men but not women (Aladin et al, 2014).

Endogenous oestrogen levels at younger ages may cause ST-segment depression similar to ischaemia (Barrett-Connor et al, 1986). Women have a longer QT interval; its duration varies during the menstrual cycle as it is affected by female hormones. Nonetheless, data from the Duke Databank for Cardiovascular Disease have shown that the increased mortality associated with a 10 ms increase in the QTc interval was significantly greater for men compared with women (4.6% *vs* 2.4%, *P*=0.004) (Williams et al, 2012). With regard to ventricular repolarization, it has been documented that women have decreased dispersion; this may contribute to the lower incidence of ventricular arrhythmias and sudden cardiac death in women with coronary artery disease (Korantzopoulos et al, 2011).

Figure 1. Coronary angiographic views of a 75-year-old woman presenting with atypical chest pain. **a.** Significant disease of the left anterior descending coronary artery with first diagonal artery bifurcation. **b.** Tight lesions in the proximal and mid right coronary artery.

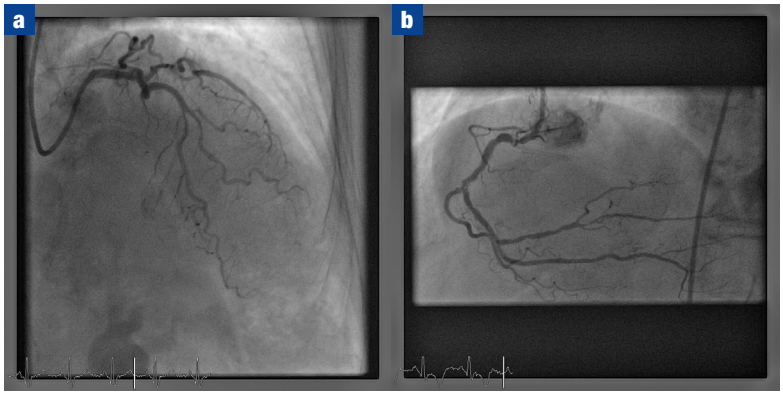
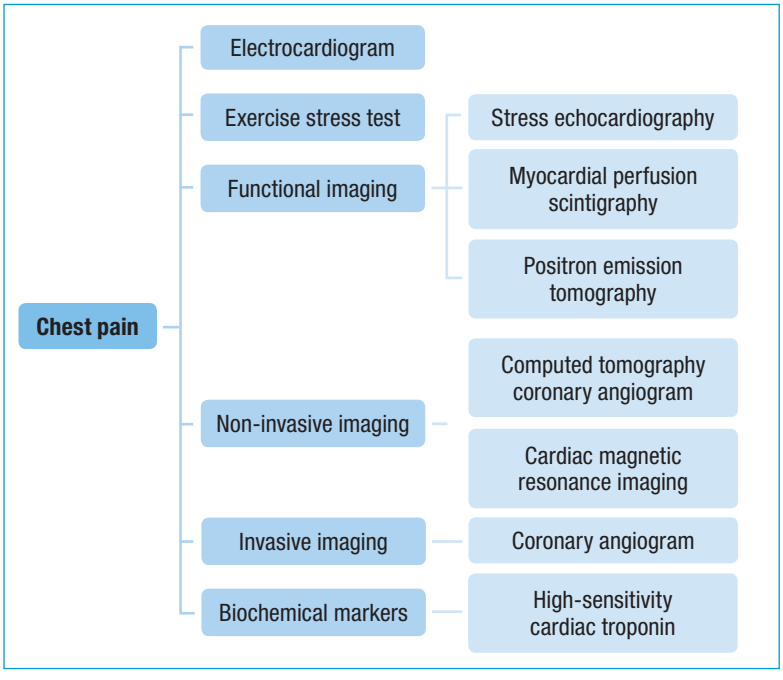


Figure 2. Diagnostic modalities used in the investigation of chest pain.



Exercise testing

Exercise stress test exhibits lower specificity and sensitivity in women, along with a high rate of false positive results. Abnormal results are linked to phases of the menstrual cycle (Lloyd et al, 2000), use of the oral contraceptive pill and use of hormone replacement therapy. Abnormal results may also be secondary to catecholamines and the higher incidence of mitral valve prolapse in women. Nonetheless, despite a high incidence of false positive tests, a low exercise capacity in symptomatic and asymptomatic women is a strong predictor of 5-year mortality (Morise et al, 2004).

Imaging

Stress echocardiography assesses regional wall motion abnormalities following tachycardia induced by drug or exercise and is more precise in diagnosing coronary artery

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disease. Echocardiography and myocardial perfusion imaging techniques have similar accuracy in both genders, and are thus recommended for the diagnosis of coronary artery disease in women.

Myocardial perfusion scintigraphy increases the diagnostic accuracy for myocardial ischaemia in women, and is crucial in the diagnosis of microvascular angina. This condition is more common in women and is diagnosed in the presence of exercise-induced perfusion defects on myocardial perfusion scintigraphy in patients with angiographically normal coronary arteries. Whereas in the past, the precision of myocardial perfusion scintigraphy was relatively low in women as a result of the presence of smaller vessels and breast attenuation, nowadays more advanced single photon emission computed tomography imaging is performed and the accuracy of results has increased significantly. Importantly, the size and severity of stress-induced perfusion abnormalities following single photon emission computed tomography predicts outcomes equally in both genders (Santos et al, 2013).

Positron emission tomography and cardiovascular magnetic resonance techniques are useful in women but are limited by their reduced availability. Calcium scoring with electron-beam computed tomography or multi-slice computed tomography is more widely available and is useful in ruling out the presence of obstructive coronary artery disease but the high dose of radiation involved limits the use of this technique in premenopausal women. However, in women older than 50 years of age who are at risk of cardiovascular disease, this calcium score is very precise in predicting the amount of coronary atherosclerosis. The use of computed tomographic coronary angiography is highly precise in identifying the cause of acute chest pain by helping to rule out pulmonary embolism and aortic dissection; however, its use is limited because of the high radiation exposure. Interestingly, computed tomographic coronary angiography findings were of limited predictive value in female patients aged <60 years compared with male patients at any age and female patients aged ≥60 years (Yiu et al, 2012).

Coronary angiography remains the gold-standard technique for the diagnosis of coronary artery disease. Fewer women with ischaemic heart disease or angina are actually referred for angiography than men. Moreover, if this study is undertaken, the results are likely to be misinterpreted as normal in women. This is because, while women have similar plaque burden to men, the plaque composition and distribution is different. This cannot be appreciated from coronary angiography which only shows the lumen of the coronary arteries; on the contrary plaque distribution can be visualized with the help of other modalities, mainly computed tomographic coronary angiography and radiofrequency intravascular ultrasound. Thus, in symptomatic patients referred for computed tomographic coronary angiography, women have a lower prevalence of obstructive coronary artery disease and are less likely to have mixed coronary plaque (i.e. calcified and non-calcified) than symptomatic men (Qureshi et al, 2013).

Plaque composition in patients with acute coronary syndrome was also assessed using intravascular ultrasound in the multicentre PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study. The researchers found that women had less extensive coronary artery disease, and lesions in women compared with men had less plaque rupture, less necrotic core and calcium, similar plaque burden and smaller lumens. The authors suggested that thin-cap fibroatheroma, as compared to thick-cap, may be a stronger marker of plaque vulnerability in women than men (Lansky et al, 2012).

Microvascular dysfunction also plays a major role as evidenced by similar extent of left ventricular myocardial ischaemia in both genders in a contrast echocardiography study in patients with non-ST elevation myocardial infarction. This was despite female patients having less prevalent angiographic coronary artery disease. This might explain why less severe angiographic findings in women with non-ST elevation myocardial infarction are not accompanied by lower mortality (Lønnebakken et al, 2014).

Biochemical markers

Gender differences also exist in biochemical markers. High-sensitivity cardiac troponin levels are increasingly measured in the diagnosis of non-ST elevation myocardial infarction. In the cohort of the GUSTO IV study, despite overall lower levels, cardiac troponin levels >99th percentile exhibited stronger prognostic information in women with non-ST elevation myocardial infarction compared with men. It was suggested that this is probably secondary to underlying pathophysiological differences and thus the authors concluded that women with symptoms of unstable coronary artery disease are at higher risk of future cardiovascular events than men (Eggers et al, 2014).

Therapeutic strategies

Both medical and interventional treatment responses are different between men and women and this partly accounts for the varying outcomes, with women having a worse prognosis following acute coronary syndrome throughout all age groups (Prata et al, 2014). As women usually have a lower body weight and higher body fat content, there are discrepancies in drug metabolism between men and women and this is usually related to the cytochrome P450 system. Furthermore, women

who have had a myocardial infarction are less likely to receive adequate treatment than men (Mehta et al, 2016). Women have also been grossly under-represented in major clinical trials and thus there is less evidence-based preventive, diagnostic and therapeutic data.

The drug response difference between genders is clearly demonstrated in the use of aspirin in primary prevention. Aspirin is highly effective in preventing myocardial infarction in men (risk reduction of 44%) but has not been proven to be of benefit in women, although some preliminary data from the Women's Health Study (Ridker et al, 2005) suggest that it may be beneficial in stroke prevention.

During the past 10 years, survival post-myocardial infarction has significantly increased, partly as a result of the use of thrombolytics, e.g. tissue plasminogen activator. Nonetheless, generally fewer women are found to be eligible to receive thrombolytics and of those who were considered eligible, a smaller percentage actually received the drug compared to men. Hence, increased public awareness is needed to ensure that women present early to hospital after experiencing chest pain, since these drugs work best when taken in the first hour after experiencing a myocardial infarction. Unfortunately, however, thrombolytics do not improve women's survival rate to the same extent as men. This could be the result of a higher rate of bleeding complications in women following thrombolysis together with a higher mean age at presentation and the presence of comorbidities, mainly diabetes, hypertension and renal failure.

Revascularization

Revascularization via percutaneous coronary intervention is the recommended treatment with regard to prognostic benefit in both ST-segment elevation myocardial infarction and non-ST elevation myocardial infarction, provided it can be performed within an adequate time frame; it provides symptomatic benefit in stable coronary artery disease.

Contradictory data exist with regard to the outcome following percutaneous coronary intervention in women. Higher in-hospital mortality was noted in women in the Belgian Working Group on Interventional Cardiology registry comprising 130 985 procedures, even after adjusting for possible confounders (Lempereur et al, 2014). In a multihospital nationwide registry of 31 869 patients, the higher total in-hospital mortality rate in women following ST-segment elevation myocardial infarction appeared to be the result of differences in age and comorbidities rather than of gender itself (Kytö et al, 2015). Similarly, in the Malaysian National Cardiovascular Disease Database –Percutaneous Coronary Intervention Registry, in-hospital and 6-month mortality for all percutaneous coronary intervention, ST-segment elevation myocardial infarction and non-ST elevation myocardial infarction were higher largely as a result of significantly more left main-stem disease, smaller diameter vessels, longer door-to-balloon and transfer time in women (Lee et al, 2013).

> **"Women undergoing coronary artery bypass graft surgery are at higher risk of left ventricular diastolic dysfunction than men; a significant age–gender interaction has been demonstrated"**

While women fared worse with the use of bare metal stents, data indicate that this difference in outcome has been eliminated with the use of drug-eluting stents (Ogita et al, 2011; Kovacic et al, 2012). In fact, in women and men with similarly-sized large coronary arteries, drug-eluting stents reduced 2-year major adverse cardiovascular event rates compared to bare metal stents, with a significantly greater benefit of drug-eluting stents seen in women (Hansen et al, 2013). Even in stable coronary artery disease, similar outcomes have been noted in the two genders in the large CLARIFY trial comprising 30 977 patients (Steg et al, 2012). More research is needed to address gender determinants of outcome and to try and minimize bias in the management of women.

Antiplatelet agents

The effect of gender in the response to antiplatelet agents in secondary prevention is still poorly defined. In fact, women may not achieve the same cardioprotective benefits from aspirin as men (Ridker et al, 2005). However, the meta-analysis of Berger et al (2006) found no gender difference following multivariate adjustment. There is similar debate with regard to clopidogrel use. In the CURE trial, the use of aspirin and clopidogrel resulted in a smaller reduction of the risk of major adverse cardiovascular events in women than men (12% *vs* 25%) (Budaj et al, 2002). On the other hand, Breet et al (2011) showed that, despite increased platelet reactivity in women, this did not result in a higher rate of poor clopidogrel responders or an increased risk of ischaemic events following percutaneous coronary intervention.

Finally, with regard to the adenosine diphosphate-antagonist ticagrelor, in a meta-analysis including 445 patients on maintenance ticagrelor therapy, gender did not emerge as an independent predictor of higher platelet reactivity (Alexopoulos et al, 2014). Nonetheless, further studies are needed to fully assess the role of gender on platelet reactivity with the use of the newer antiplatelet agents.

Coronary artery bypass grafting

Coronary artery bypass grafting has historically demonstrated higher in-hospital mortality in women compared to men. This is especially true in the younger age groups, where the mortality risk is around three times worse than in men (Vaccarino et al, 2002). This may be attributed to smaller body size, smaller vessel size or more emergency

KEY POINTS

- Cardiovascular disease is the leading cause of death in women, amounting to 8.6 million deaths per year worldwide.
- Women with coronary artery disease are more likely to present with atypical symptomatology, including abdominal pain, shortness of breath, back and neck pain, indigestion, nausea or vomiting, palpitations and fatigue.
- In terms of diagnosis, exercise testing is less reliable in women, stress echocardiography and myocardial perfusion imaging have similar accuracy in both genders, while coronary angiography is more likely to be misinterpreted as normal in women as they show different plaque distribution.
- Gender differences are seen in secondary prevention with women less likely to achieve optimal low density lipoprotein and non-high density lipoprotein cholesterol goals. A difference in survival has also been noted following implantable cardioverter defibrillator implantation in patients with ischaemic cardiomyopathy.
- More studies are needed to assess the gender differences in diagnosis, preventive and therapeutic management and underlying pathophysiology, and clinical trials should be designed to consider gender effects.

procedures in women, as well as an increasing number of comorbidities in women. The microvasculature may have a more important role in women and problems may arise here more often in women than men. Furthermore, women undergoing coronary artery bypass graft surgery are at higher risk of left ventricular diastolic dysfunction than men; a significant age–gender interaction has been demonstrated by Ferreira et al (2014), suggesting a possible age-related differential effect on left ventricular diastolic dysfunction between the genders. Interestingly, in a retrospective analysis of 4584 consecutive coronary artery bypass graft patients, Kurlansky et al (2013) demonstrated that the use of bilateral internal mammary artery grafting as opposed to single internal mammary artery grafting improved perioperative outcome in women as well as improving long-term survival of male patients. The authors concluded that the liberal use of bilateral internal mammary artery effectively reversed the negative influence of gender on both short- and long-term outcomes of coronary artery bypass graft surgery.

Secondary prevention

Both cardiac rehabilitation and medical therapy play a crucial role in secondary prevention of cardiovascular events. A comprehensive cardiac rehabilitation programme performed under supervision of a physician and an exercise physiologist results in significant improvement in the functional capacity and lipid profiles of non-obese subjects with coronary artery disease, irrespective of gender (Sadeghi et al, 2012). With regard to medical treatment, reduction of low density lipoprotein-cholesterol levels with the use of statins reduces the risk of coronary artery disease mortality in men and women equally. However, data indicate that women with coronary artery disease are prescribed insufficient doses of statins and combination lipid-lowering therapy (Victor et al, 2014). Furthermore, they are less likely to achieve their optimal low density lipoprotein and non-high density lipoprotein cholesterol goals (Singh et al, 2013; Victor et al, 2014), indicating the need for more aggressive lipid-lowering strategies in women.

A gender-based difference in survival has also been noted following implantable cardioverter defibrillator implantation in patients with ischaemic cardiomyopathy. Men with larger myocardial scar burden have significant survival benefit with implantable cardioverter defibrillators, whereas men with smaller myocardial scar burden derive limited benefit from them. However, the inverse relationship was found in women. Further studies are needed to investigate the underlying pathophysiology (Kwon et al, 2014).

Conclusions

Although men and women share various risk factors, symptom presentation and outcomes are different. Future research should focus on how these differences affect both preventive and therapeutic strategies. While women should be encouraged to take part in surveys and enrol in major research projects, major clinical trials should be designed in such a way that they consider the gender dimension. Further studies focusing on gender differences in drug therapy should also be encouraged. Until these aspects are considered, there will continue to be disparities in delivery of care between genders.

Women should be advised of their risk of cardiovascular disease and symptom presentation both by health-care providers and government entities. More emphasis should be given to adequate health promotion. A multidisciplinary approach is required and physicians need to increase their awareness of the differences between the two genders and their effect on health. This will ensure that the inequity in cardiac health care currently being provided to women worldwide will be overcome and the myth of the apparent 'immunity' of women to cardiovascular disease will be abolished. **BJHM**

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