Coronary artery disease
in women

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Educational aims
- To better appreciate the importance of coronary artery disease in the female population
- To shed light on the complex effect of oestrogen on the cardiovascular system
- To highlight the importance of non-invasive testing in women at intermediate risk for ischaemic heart disease
- To identify gender differences in medical and interventional management of acute coronary syndrome

Key words
Coronary artery disease, women, oestrogen effects, exercise stress testing, drug eluting stents

Abstract
Up to some decades ago, coronary artery disease (CAD) has been thought of as being a predominantly ‘male disease’. Population studies have however shown, that CAD is the major cause of death in females, surpassing six-fold the death rate due to breast carcinoma. Post-menopausally, ischaemic heart disease (IHD) in women is as common as in males of the same age group. Hence, the investigation and management of females with CAD is vital, in order to decrease the mortality in the female population.
Women are generally older than men when they develop IHD and have multiple co-morbidities. Hypertension, diabetes mellitus and renal impairment are more frequent among females. After menopause, the level of low-density lipoprotein (LDL)-cholesterol increases whilst the level of high-density lipoprotein (HDL)-cholesterol decreases. All these factors contribute to a high incidence of CAD, especially in post-menopausal women. Higher rates of hypertension, left ventricular hypertrophy, and diabetes in women, are hypothesized to result in a greater degree of microvascular rather than macrovascular disease.

Symptoms of CAD
Numerous observational studies have suggested that symptoms of myocardial ischaemia differ in the two sexes. Women were more likely to present with angina at the onset of IHD, whereas men often present with an acute myocardial infarction (AMI) or sudden cardiac death. An objective study performed by Mackay et al, involved performing percutaneous coronary intervention (PCI) in a cohort of male and female patients with CAD. Ischaemic symptoms were assessed during prolonged balloon inflation. No statistical significant difference was seen in the frequency of ischaemia-induced chest discomfort among women versus men. However, females were significantly more likely to report throat, jaw and neck discomfort. On the other hand, females experiencing an AMI, are more likely to have atypical symptoms such as shortness of breath, abdominal, neck, or should pain, or nausea and vomiting.

Exercise stress testing in women
Exercise stress testing (EST) is one of the most commonly used method of investigating for CAD in women and is the initial non-invasive test of choice in women with a moderate to high pre-test probability of having CHD. EST however is known to be less sensitive and less specific in the female population resulting in a number of false positive results. Differences in the accuracy of ST-segment depression for men and women may be explained by several factors. Women are more likely than men to have baseline ST-T wave changes, making interpretation of ECG changes during exercise difficult. It has also been hypothesised that oestrogen (natural or otherwise), may cause a digoxin-like effect on the ST segments during exercise. In premenopausal women with no CAD, ST depressions during exercise appear to vary with the menstrual cycle.

Despite this, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, still recommend EST as the first line test for symptomatic women, who are deemed at intermediate risk for IHD and who have a normal baseline ECG and are capable of performing maximal exercise. The diagnostic and prognostic accuracy of EST in women can be improved by incorporating parameters such as exercise capacity, chronotropic response, heart rate recovery, blood pressure response and Duke treadmill score, in addition to ST depression during exercise. The duration of metabolic equivalents (METS) is the strongest prognostic variable with a higher death rate in women who can achieve less than 5 METs. Stress echocardiography, and myocardial perfusion imaging further contribute to the diagnosis of IHD in women. CT coronary angiography is another non-invasive tool used to assess for obstructive CAD in women, with a similar diagnostic sensitivity and specificity in both genders.

Gender differences in the management of CAD
Female patients with CAD tend to be older and have poorer risk profiles than their male counterparts. This has resulted in the exclusion of women from participation in past clinical trials, reducing their power to detect differences in outcomes between the two sexes. In recent years, the recruitment of female patients in clinical trials has increased, shedding more light on the clinical outcomes of the different therapeutic strategies in males and females.

Medical management
Women with an AMI are more likely to develop complications such as bleeding, cardiogenic shock, heart failure, stroke and re-infarction. The medical management of AMI often includes thrombolysis (in the setting of ST-elevation MI), heparin, anti-platelet therapy, beta-blockers, statins and ACE-inhibitors. Data on thrombolysis and gender differences is somewhat contradictory. In the International Tissue Plasminogen Activator /Streptokinase Mortality study, mortality was found to be similar in both sexes with women however having a higher rate of haemorrhagic stroke. Females are more likely to achieve a higher activated thromboplastin time after administration of unfractionated heparin. A greater reduction in mortality rate and myocardial infarction was seen in females after administration of dalteparin as compared to males. Similarly in the TIMI and the ESSENCE trials, a significant benefit of enoxaparin over unfractionated heparin was seen in women but not in men. No sex-related differences were seen in trials with bivalirudin and fondaparinux.

A metaanalysis of randomized trials has shown that glycoprotein IIb/IIIa receptor antagonists gave a significant increased bleeding risk in women. However, if the baseline troponin levels were high, then beneficial effects were seen in both sexes. There were no sex differences in the response to aspirin, ticlopidine, clopidogrel and prasugrel. A more pronounced decrease in heart rate and blood pressure was seen in women on beta-blockers and ACE-inhibitors compared to men.

Coronary revascularization
Women with CAD are often older, obese, suffer more from diabetes and hypertension, generally smoke, may have had a previous cardiac event and surgical revascularization, and usually have a smaller reference diameter of the target vessel as well as a lower Syntax Score compared to men. Earlier studies during the balloon angioplasty era reported a lower procedural success, a higher in-hospital mortality and unfavourable long term clinical outcomes among women. The unrestricted use of drug eluting stents (DES) in more recent years, is now associated with similar long-term safety and efficacy among women and men with CAD. The similar outcomes in terms of cardiac death, myocardial infarction and stent thrombosis are reassuring and reinforce the lack of sex difference in terms of patient outcome and device safety.

Generally women have a higher mortality risk after coronary artery bypass graft (CABG) than men. In fact, in-hospital mortality after CABG has been shown to be twice as high in women as compared to men. The more advanced age, smaller body size, smaller coronary lumen, and higher incidence of comorbidities all contribute to this. Women have a more difficult recovery period after CABG. On the other hand, The Bypass Angioplasty Revascularisation Investigation (BARI) group observed no gender differences in early or late mortality after percutaneous transluminal angioplasty (PTCA) and CABG.

Conclusion
This review gives insight to the complexity in the pathophysiology, assessment and management of CAD in women. The inclusion of more female patients in clinical trials, will definitely shed more light on the extent of gender differences in CAD. Future research may help clarify the intricate effects of oestrogen on the human heart.
References


Key points

- IHD is the leading cause of death in the female population.
- The cardioprotective mechanism of oestrogen is still unclear.
- Female patients with CAD are often older and have multiple co-morbidities.
- Exercise stress testing should be performed in females with moderate pre-test probability of IHD.
- Further clinical trials are needed to clarify how best to treat female patients with CAD.


