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.

Introduction

The importance of CAD in women has been underestimated for many years.[1] Currently, IHD is responsible for the death of approximately 400,000 women annually in the US alone, making CAD the leading cause of death in females.[2] There are fundamental differences between male and female hearts with regard to electrophysiology, contractility, signalling, metabolism, and cardioprotection. Differences in cardiomyocytes likely contribute to the differences in male and female physiology and response to disease.[3] Pre-menopausal women have less cardiovascular disease compared to men, yet the incidence of IHD in females rises after menopause.

Pathophysiology of CAD in women

Studies investigating sex-related differences in the cardiovascular system were lacking up to some years ago, but fortunately the number of clinical and experimental studies has grown exponentially over the past 20 years. These studies have shown that the onset of IHD occurs approximately 10 years later in women than in men, with myocardial infarction occurring around 20 years later.[4] The incidence of CAD increases dramatically in post-menopausal women, suggesting that the decline in oestrogen levels may be a major contributing factor to this increase. Oestrogen has a number of effects on cardiovascular function and disease: it modulates vascular function and the inflammatory response, it affects metabolism, insulin sensitivity and calcium handling in cardiac myocytes, it influences stem cell survival and the development of left ventricular hypertrophy.[5] The exact underlying molecular and cellular mechanisms by which oestrogen exerts its cardioprotective effects on myocytes, are still largely unknown, but it is speculated that oestrogen may affect gene and protein expression and may modify post-translational proteins.[3] One would assume that hormone replacement therapy (HRT) would decrease the incidence of CAD in women. However data is unclear, with groups suggesting the 'Therapeutic Window' theory, reinforcing the complex role of oestrogen on cardiac function.[6,7,8]

The Women's Ischaemia Evaluation (WISE) trial and other studies have shed further light on the complex pathophysiology of coronary atherosclerosis in females which includes abnormal coronary reactivity, microvascular dysfunction and plaque erosion with distal microembolisation.[9] Obstetric complications such as pre-eclampsia, gestational diabetes and pregnancy-induced hypertension, are early indicators of cardiovascular risk.[10]

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.[11] 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. [12]

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.[13] On the other hand, females experiencing an AMI, are more likely to have atypical symptoms such as shortness of breath, abdominal, neck, or shoulder pain, or nausea and vomiting. [14]

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.[15] 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.[16] 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. [17]

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. [18,19] 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.[20] 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.[21] 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.[22]

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.[23] 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.[1] 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.[24] 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. [25] Females are more likely to achieve a higher activated thromboplastin time after administration of unfractionated heparin.[26] A greater reduction in mortality rate and myocardial infarction was seen in females after administration of dalteparin as compared to males.[27] Similarly in the TIMI and the ESSENCE trials, a significant benefit of enoxaparin over unfractionated heparin was seen in women but not in men.[28] No sex-related differences were seen in trials with bivalirudin [29] and fondaparinux. [30]

A metanalysis of randomized trials has shown that glycoprotein IIb/IIIa receptor antagonists gave a significant increased bleeding risk in women. [31] However, if the baseline troponin levels were high, then beneficial effects were seen in both sexes.[32] There were no sex differences in the response to aspirin, ticlopidine, clopidogrel and prasugrel.[33, 34] A more pronounced decrease in heart rate and blood pressure was seen in women on beta-blockers and ACE-inhibitors compared to men.[35]

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. [36] 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. [37]

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.[38] 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.[39] 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. [40]

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

1. Tillmanns H, Waas W, Voss R, Grempels E, Holschermann H, Haberbosch W, Waldecker B. Gender differences in the outcome of cardiac interventions. Herz 2005; 30:375-89.
2. Singh M, Rihal CS, Gersh BJ, Roger VL, Bell MR, Lennon RJ, Lerman A, Holmes Jr DR. Mortality differences between men and women after percutaneous coronary interventions - a 25-year single-center experience. J Am Coll Cardiol 2008; 51:2313-20.
3. Murphy E, Steenburgen C. Estrogen regulation of protein expression and signalling pathways in the heart. Biology of Sex Differences 2014, 5:6.
4. Bassuk SS, Manson JE (2010). Gender- specific aspects of selected coronary heart disease risk factors: a summary of the epidemiological evidence. In: Legato MJ (ed). Principles of Gender-Specific Medicine. Elsevier inc: Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San diego, San Francisco, Singapore, Sydney, Tokyo, pp.162-174.
5. Murphy E. Estrogen signaling and cardiovascular disease. Circ Res (2011) 75:478-486.
6. Hulley S, Grandy D, Bush T,Furbek C, Herrington D, Riggs B et al. Randomised trial of oestrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998 280:605-612.
7. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE et al. Effects of oestrogen replacement on the progression of coronary-artery atherosclerosis. NEJM 2000 343:522-529
8. Rossouw JE, Anderson GI, Prentice RL, LaCroix AZ, Kooperberg CH, Hutchinson F et al. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized control trial. JAMA 2002 288:321-333.
9. Bairey-Merez CN, Shaw LJ, Reis SE et al. Insights from the NHLBI-Sponsored Women's Ischaemia Syndrome Evaluation (WISE) study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006 ;47(3 Suppl): S21-9.
10. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular Health After Maternal Placental Syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005; 366 :1797–1803.
11. Rossi R, Grimaldi T, Origliani G, Fantini G, Coppi F, Modena MG. Menopause and cardiovascular risk. Pathophysiol Haemost Thromb 2002; 32: 325-8.
12. Shaw LJ, Bugiardini R, Merz CN, Women and Ischaemic Heart disease: evolving knowledge. J Am Coll Cardiol.2009; 54:1561-75.
13. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. European Heart Journal (2011); 32:3107-3114.
14. Wenger NK. Clinical characteristics of coronary heart disease in women: emphasis on gender differences. Cardiovasc Res 2002; 53:558-67.
15. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. American Heart Journal 1995; 130:741-747.
16. Higgins JP, Higgins JA. Electrocardiographic exercise stress testing: an update beyond the ST segment. Int J Cardiol. 2007; 116:285-299.

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.

17. Mora S, Redberg RF, Whiteman MK, Flaws JA, Sharett AR, Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20 - year follow-up of the Lipid Research Clinics Prevalence study. JAMA 2003; 290:1600-1607.
18. Fihn SD et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/SCAI/STS **Guideline** for the diagnosis and management of patients with **stable** ischemic heart **disease**: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice **Guidelines**, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012 Dec 18; 60(24): e44-e164.
19. Montalescot G et al. 2013 ESC **guidelines** on the management of **stable coronary artery disease**: the Task Force on the management of **stable coronary artery disease** of the European Society of Cardiology. Eur Heart J. 2013 Oct; 34(38): 2949-3003.
20. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. Circulation 2010; 122:2570-80.
21. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St jmaes Women Take heart project. Circulation 2003; 108:1554-9.
22. Pundziute G, Schuijf JD, Jukema JW, et al. Gender influence on the diagnostic accuracy of 64-slice multi-slice computed tomography coronary angiography for detection of obstructive coronary artery disease. . Heart 2008; 94:48-52.
23. Lee TM, Poh KK, Tang TP, Tan YL, Tee HW, Tan HC. The impact of gender on the outcomes of invasive versus conservative management of patients with non-ST-segment elevation myocardial infarction. Ann Acad Med Singapore 2010 39:168-172.
24. Nicolau JC, Auxiliadora Ferraz M, Nogueira PR, Coimbra Garzon A, Serrano CV, Jr, Ramires JA. The role of gender in the long-term prognosis of patients with myocardial infarction submitted to fibrinolytic treatment. Ann Epidemiol 14:17-23.
25. White HD, Barbash GI, Modan M, Simes J, Diaz R, Hampton JR et al. After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of heamorrhagic stroke. The investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality study. Circulation 1993 88:2097-2103.
26. Granger CB, Hirsch J, Califf RM, Col J, White HD, Betriu A et al. activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. Circulation (1996) 93:870-878.
27. FRISC Study group. Low molecular-weight heparin during instability in coronary artery disease. Fragmin during instability in coronary artery disease (FRISC) study group. Lancet 1996 347:561-568.
28. Cohen M, Antman EM, Gurfinkel EP, Radley D. Enoxaparin in unstable angina/non-ST-segment elevation myocardial infarction: treatment benefits in prespecified subgroups. J Thromb Thrombolysis 2001 12: 199-206.
29. Stone GW, White HD, Ohman EM, Bertrand ME, Lincoff AM, Mclaurin BT et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterisation and Urgent Intervention Triage strategy (ACUITY) trial. Lancet 2007 369:907-919.
30. Madsen JK, Chevalier B, Darius H, Rutsh W, Wojcik J, Schneider S,et al. Ischaemic events and bleeding in patients undergoing percutaneous coronary intervention with concomitant bivalirudin treatment. Eurointervention 2008 3:610-616.
31. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van der Werf et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised trials. Lancet 2002; 359: 189-198
32. Capodanno D, Angiolillo DJ. Impact of race and gender on anti-thrombotic therapy. Thromb Haemost 2010 104:471-484.
33. Becker DM, Segal J, Vaidya D, Yanek LR, Herrera-Gaetano JE, Bray PF et al. Sex differences in platelet reactivity and response to low-dose aspirin therapy. JAMA 2006 295:1420-1427.
34. Jochmann N, Stang K, Garbe E, Baumann G, Stangl V. Female-specific aspects I the pharmacotherapy of chronic cardiovascular diseases. Eur Heart Journal 2005 26:1585-1595.
35. Cowley MJ, Mullin SM, Kelsey SF, , et al. Sex differences in early and long-term results of coronary angioplasty in the NHLBI PTCA registry. Circulation 1985; 71:90-97.
36. Stefanini GG, Kalesan B, Pilgrim T, Raber L, Onuma, Y, Silber S, Serruys P, Meier B, Juni P, Windecker S. Impact of sex on clinical and angiographic outcomes among patients undergoing revascularization with drug-eluting stents. JACC: Cardiovascular interventions 2012: Vol 5. No.3 301-310.
37. Grines CL, Schreiber T. Sex differences in the Drug-Eluting Stent era. Do they still exist? JACC: cardiovascular interventions Vol 5 no3: 311-312.
38. Soliemene MC. Coronary Heart disease in women: a challenge for the 21st century clinics (Sao Paulo) 2010;65:99-106.
39. Vaccarino V, Abramson JL, Veledar E, Weintrub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. Circulation 2002; 105:1176-81.
40. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, Mock MB, Weiner BH, Dean L, Winston C, drew L, Sopko G. Better outcome for women compared with men undergoing coronary revascularisation: a report from the Bypass Angioplasty Revascularisation Investigation (BARI). Circulation 1998; 98:1279-85.