Jurnal
Kardiologi Indonesia
J Kardiol Ind 2007; 28:224-228
ISSN 0126/3773

Literature Review

Women Make the Difference in Heart Disease

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Cardiovascular disease develops 10 to15 years later in women than in men and is the major cause of death in women older than 65 years of age. The risk of heart disease in women however is still underestimated and many women are not aware of their own risk factors. In a recent report from the European Heart Survey on stable angina pectoris it was found that women are less likely to be referred for functional testing for ischemia, with a lower rate of diagnostic angiograms and interventional procedures.[1]

The under-recognition of heart disease and differences in clinical presentation in women lead to less aggressive treatment strategies and a lower representation of women in clinical trials. In the current review we summarize the major issues that are important in the diagnosis and treatment of coronary heart disease (CHD) in women.

Epidemiology and role of menopause

Women with an acute myocardial infarction (AMI) are in general older than men, with a higher mortality and a larger co-morbidity in coronary heart disease risk factors.[2-4] It is assumed that exposure to endogenous estrogens during the fertile period of life delays the manifestation of atherosclerotic disease in women. Before menopause the CHD event rate in women is low and predominantly attributed to smoking.[5] Women with early menopause (< 40 years) have a 2–years lower life-expectancy compared with women with a normal or late menopause.[6] Young women with endogenous estrogen deficiency have a > 7 fold increase in coronary artery risk.[7] Estrogens have a regulating effect on several metabolic factors, such as lipids, inflammatory markers and the thrombotic system. They also promote a direct vasodilatory effect on the α and β-receptors in the vessel wall.[8] Premenopausal women with CHD have lower estrogen levels than healthy women. After menopause atherosclerotic plaque composition changes into more vulnerable lesions with inflammatory factors involved.[9]

Male/female differences in CHD risk factors

Although women and men share most classic atherogenic risk factors, the significance and the relative weighting of these factors are different. At younger ages (<50 years) ***smoking*** is more deleterious in women than in men, with a greater negative impact of the total number of cigarettes smoked per day.[5,10] Heavy female smokers also have a 2 years earlier onset of menopause. Central ***obesity*** with an increase in visceral fat occurs more frequently after menopause, with a higher presence of co-morbid risk factors and components of the metabolic syndrome in women compared with men[11]. Women diagnosed with the polycystic ovary syndrome are at increased risk of the metabolic syndrome and of type 2 diabetes mellitus.[12]

Women with ***diabetes*** are at greater risk for cardiovascular complications than their male counterparts. In a recent meta-analysis of 37 prospective cohort studies, the risk of fatal CHD is

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50% higher in women compared with men.[13] The reason for this higher mortality is multifactorial and related to a heavier risk factor burden, more involvement of inflammatory factors, a smaller vessel size of the coronary arteries and often a less aggressive treatment of diabetes.[14] At older age (> 75 years) isolated systolic *hypertension* is 14% more prevalent in women and an important cause of left ventricular hypertrophy and (diastolic) heart failure. Moderate or borderline hypertension (< 140/90 mmHg) causes more cardiovascular complications and endothelial dysfunction in women than in men[15]. Hypertension often starts in the menopausal transition period and can cause a variety of complaints, such as chest pain, palpitations, headaches and even sensations of hot flashes. Women with a history of hypertensive diseases in pregnancy are at increased risk for hypertension and premature cardiovascular disease.[16,17]

The relative risk of *hypercholesterolemia* is lower in women below 65 years of age compared with men. In the menopause transition total cholesterol levels rise 10%, low-density lipoprotein (LDL) cholesterol rises 14% and lipoprotein (a) increases 4 to 8%, whereas high-density lipoprotein (HDL) cholesterol levels remain unchanged.[18] Therefore it may be important to (re)evaluate the lipid profile after menopause. The efficacy of statin therapy in women has been disputed, but seems similar in risk reduction in both gender.[19]

Recently, an update on the guidelines for CHD risk reduction has been published that underscores the importance of lifestyle measurements in primary prevention in women.[20] More than 80% of all cases of CHD in women can be prevented through a healthy life-style.[21]

Clinical presentation and non-invasive testing for angina pectoris

The clinical presentation of coronary heart disease and non-invasive diagnostic testing is less reliable in women compared with men, especially in the age-group below 55 years when the prevalence of coronary artery disease is still relatively low. [22,23]

There are no gender-specific criteria for the interpretation of ECG's, although women have a higher heart-rate at rest with a longer QT-interval. Non-specific ECG changes at rest, a lower exercise capacity and a smaller vessel size contribute to the lower sensitivity and specificity of non-invasive testing in women. At younger ages, endogenous estrogen levels can induce ECG-changes. Female-specific normograms have been developed for *treadmill exercise* testing.[24] A low exercise capacity in symptomatic as well as in asymptomatic women is a strong predictor of 5-years mortality. *Stress echocardiography* with exercise or dobutamine can be an important test to predict the presence of CHD and its clinical value is not different within both gender.

The accuracy of *myocardial perfusion imaging* scans used to be less in women due to smaller vessel size and over-projection of the breasts, but with more advanced SPECT imaging techniques with Technetium sestimibi the predictive value of the scans have improved dramatically.[25] *Calcium scoring* with EBTC or multi-slice CT is a rapid developing modality to predict the presence of atherosclerotic disease. The amount of calcium found in the coronary arteries is a strong predictor of plaque burden. In women at intermediate risk for CHD the absence of coronary calcium has a very high negative predictive value (99%) of coronary artery disease.[26] In all age groups calcium scores are lower in women than in men.[27]

Acute coronary syndromes in women

In acute coronary syndromes (ACS), both men and women have similar symptoms of chest pain, but women tend to have more concomitant vaso-vegetative symptoms with less extensive ST-T elevations at admission, especially at younger ages.[3] Women under 55 years are therefore often misdiagnosed at the emergency department [28]. In general, women with ACS are older with more clustering of risk factors that contribute to their higher risk in mortality.[3,4,29,30] Gender bias in treatment and gender disparities in vascular flow and structure may further add to this increased mortality.[31,32] Other aspects that may account for differences in vascular biology between women and men are related to a smaller vessel size, less collateral flow, more vascular stiffness, differences in remodeling, and the function of smooth muscle cells in the vessel wall. An interesting observation is that women with ACS have less obstructive coronary artery disease compared with men, but the event rate in non-obstructive coronary artery disease seems to be higher in women.[33] Especially young women have more often ACS with angiographically normal coronary arteries than men.[3.34] The underlying mechanisms are diverse (e.g. microvascular dysfunction, disturbances in

vascular reactivity, low endogenous estrogen levels, coagulation disorders, abnormal inflammatory reactions etc. and may have a substantial variability among individuals.[35] The prognosis of these syndromes is less beneficial than initially thought.[36]

Gender differences after coronary interventions and heart failure

Gender differences in mortality after coronary artery bypass surgery (CABG) is higher in women compared with men, and this difference is more pronounced in the younger age groups.[37,38] Many factors influence this gender gap, such as co-morbid conditions at older age, smaller vessel size, more urgent procedures in women and hypertensive heart disease. Furthermore, women have significantly more bleeding complications after percutaneous coronary interventions (PCI).[39]

Heart failure due to ischemic heart disease is more prevalent in men, while diastolic heart failure with a preserved ejection fraction occurs more often in women.[40] At older age, women have more left ventricular hypertrophy due to hypertension than men. The lack of estrogen in postmenopausal women may also contribute to the increase in ventricular mass that is seen in women at older age.[41]

Menopausal hormone therapy and CHD risk

Despite the benefits of hormonal therapy (HT) that have been shown in observational studies, randomized trials have failed to show any benefit.[42] In most observational studies, however, women started HT for menopausal symptoms, whereas in experimental studies women started HT 10 to 20 years after menopause. Initiation of HT after a recent coronary event results in an early increase in adverse events.[43] Proinflammatory effects of HT on advanced atherosclerotic lesions are assumed to contribute to the progression of CHD when present. Data from the Women's Health Initiative have shown that HT is not beneficial in primary prevention either, but it has not been proven harmful on the vascular system in healthy women during their early postmenopausal years.[44,45] Recent guidelines have been postulated for the use of HT in the peri-and postmenopause.[46] Many determinants of vasomotor symptoms overlap with CHD risk factors, such as smoking, obesity, hypertension, lack of exercise and excessive alcohol use. Life-style measurements are therefore of primary importance in the treatment of perimenopausal symptoms.

Conclusion

A greater awareness of the many epidemiological and biological differences that exist between men and women may improve our treatment success of CHD patients in daily practice.

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