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Review Article

Caronary Artery Disease in Women

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Abstract

Coronary artery disease (CAD) - which includes coronary atherosclerotic disease, myocardial infarction (MI), acute coronary syndrome and angina - is the most prevalent form of cardiovascular disease and is the largest subset of this mortality. Coronary artery disease (CAD) is a leading cause of death of women and men worldwide. CAD's impact on women traditionally has been underappreciated due to higher rates at younger ages in men. Microvascular coronary disease disproportionately affects women. Women have unique risk factors for CAD, including those related to pregnancy and autoimmune disease.

Key Words: *Coronary artery disease (CAD); Myocardial infarction*

Introduction

Coronary artery disease has been widely considered a "man's disease" and not a major concern for women. Yet cardiovascular disease is the leading cause of death in adult women. During the fertile age, women have a lower incidence of CAD, but aftermenopause the incidence is the same or higher. Although mortality from ischaemic heart disease (IHD) has declined in the recent years, the decline observed is of lesser magnitude in women as compared to men of a similar age.[1] Over the past two decades, public education efforts related to cardiovascular disease prevention have been aimed primarily at male populations. As a result, the prevalence of coronary risk factors and the number of cardiovascular deaths have decreased in men—but not in women.[2]

Currently available guidelines and systematic reviews provide specific treatment recommendations for women. However, women have a worse prognosis than men for manifestations of CAD such as acute myocardial infarction. Further, women are more likely than men to experience bleeding complications. Lipid-lowering medications and hormone replacement therapy have raised great hopes for primary prevention of coronary artery disease (i.e., prevention of a first myocardial infarction or the onset of symptomatic coronary artery disease). However, in caring for women, there is a need of randomized, controlled trials to support the effectiveness of these measures. In secondary prevention, which includes measures to prevent re infarction and cardiovascular death, there is good evidence for the effectiveness of many therapies.

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Impact of gender on risk factors

While therisk factors for CAD are virtually the same in men andwomen, the impact of these risk factors is different forboth sexes.Multiple factors are likely to contribute the higher rate of cardiovascular complications among women with CAD.[4] These factors include:

- Cardiovascular disease affects women later in life.[5,6]
- When CAD is diagnosed, women mostly have comorbid factors such as diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, and heart failure.[7,8]Diabetes isa more powerful risk factor for women than for men
- Women present with angina-equivalents such as dyspnea or atypical symptoms more often than men.[9,10]
- The coronary vessels in women are smaller than those of men, which makes them more difficult to revascularize-percutaneously and surgically.[11] Also microvascular disease coronaries is commoner in women than in men.[12]
- Women tend to have less extensive CAD and a higher proportion of nonobstructive CAD.[13,14]
- Delay in hospitalization, symptom pattern and recognition, and higher frequency of nonobstructive CAD results in delay in diagnosis and treatment.[15,16]

Obesity and physical inactivity

Physical inactivity contributes to obesity and is an independent risk factor for myocardial infarction. Conversely, modest exercise has been strongly associated with risk

reduction in observational studies.[17]Obesity is an independent risk factor for all-cause mortality. It is highly associated with diabetes, hyperlipidemia and hypertension.The risk of cardiovascular disease becomes higher with increasing weight, even at lower BMIs. Central obesity (a waist-to-hip ratio greater than 0.8) is associated with a disproportionate increase in coronary risk.[18]

Hyperlipidemia

In women, low-density lipoprotein (LDL) cholesterol and total cholesterol levels increase after the age of 55 years and peak between 55 and 65 years of age, about a decade later than in men.High triglyceride levels seem to increase the risk of coronary artery disease in women.[19] Compared with men, women have slightly higher high-density lipoprotein (HDL) cholesterol levels, and these levels tend to remain steady throughout life.[20]

Smoking

Smoking is a major risk factor for the development of cardiovascular disease in women. More than 60 percent of myocardial infarctions in women younger than 50 years are attributable to smoking, as are 21 percent of all deaths from coronary artery disease.[21]All women benefit from quitting smoking. Because of gender-based differences in reasons for smoking, reasons for quitting and responses to pharmacologic agents, research on gender-specific smoking cessation strategies is needed.

Oral contraceptives[22]

The use of oral contraceptives (OC) has been associated with an increased risk of atherosclerosis as well as venous thrombosis. Many efforts have been made to lower such risks by reducing estrogen dosage and modifying the progestagen compound.When different generations of these medications were compared, the risk for AMI for those who used second-generation contraceptives was increased by a factor of 2.5 while third-generation OC did not increase the risk significantly (OR1.3), suggesting a lower risk, but the overall findings remain inconclusive. The generation is defined by type of progestagen: second generation includes levonorgestrel and third generation includes desogestrel and gestodene.

Clinical features

There are important differences in presentation of CAD between womenand men. Because angina and MI in women do nottend to conform to classic descriptions,[23,24] the presence of atypical symptoms does not decrease likelihood of CAD inwomen as it does in men.Along with exertional angina, women are more likely to experience angina painat rest, with mental stress, or during sleep.They might experience pain in locations other than theanterior chest, such as the lower jaw and teeth, arms, shoulders, back and epigastrium.[25]Women are more likely to have dyspnea, palpitations, presyncope, fatigue or vomiting as chestpain equivalents and also experience moresilent MIs;nearly half of women's MIs are unrecognised.[26]

Unstable angina (UA) is defined as angina with at least one of three features: (1) it occurs at rest or with minimal exertion, (2) it is severe and of recent onset (within the past 4 to 6 weeks), and/or (3) it occurs in a crescendo pattern (i.e., more severe, more prolonged, or more frequent than previously experienced). UA and NSTEMI have a fairly similar pathophysiology, mortality rate, and management strategy when compared with STEMI; therefore they are often grouped together as UA/NSTEMI in clinical guidelines and trial populations. Chronic stable angina is classified as pain that classically occurs with moderate to severe exertion, is milder in nature, and is relieved with rest or sublingual nitroglycerin.

Pathophysiology

There are some basic differences with respect to the pathogenesis of CAD in women as compared to men. Basic difference lies in the pattern of vascular diseasein women. Structurally, their coronary vessels contain more diffuse atherosclerosis with involvement ofthe entire circumference of the artery. There is paucity of localisedplaques. Thus, in response to atherosclerosis,there is entire remodelling of artery so that the lining of the arterybecomes thickened throughout, making the plaques flushwith the wall of the artery ("Female-pattern" coronary artery disease).[27]

In the study done by Masery et al,[28]unstable angina carries a much more severe prognosis than chronic stable angina. Also the angina does not carry an increased risk of infarction or sudden cardiac death. Syndrome X is a typical condition that illustrates the challenge of the diagnosis of myocardial ischemia. It has a 10%-15% incidence in patients submitted to coronary angiography and is characterized as angina pectoris and normal coronary angiography. Such criteria include heterogeneous patients with and without cardiac origin of pain, which turns diagnosis of myocardial ischemia even more difficult.

WISE study[29]have shown thepathophysiologic role of microvascular and endothelial dysfunction in CAD in females. On an average, they have coronary vessels 10% smaller than those in men. Functionally, their vessels frequently show impairedvasodilator responses.[30]In such women, ischaemic injury may not be limited because the usual vasorelaxation required for collateral function is abnormal.

Diagnosis

Non-invasive diagnostic studies (exercise ECG and cardiac imaging studies) are recommended for women older than 50 years with risk factors like diabetes and metabolic syndrome.[31]The exercise ECG has a lower sensitivity for women (with more false positives) than for men.

Also, treadmill testing has lesser diagnostic value in women as compared to men. Myocardial perfusion imaging is more specific than exercise testing, especially with technetium 99m sestamibiSPECT imaging. Stress echocardiography in women shows comparable sensitivity and specificity to studies in men and is a valuable test as long as an adequate echocardiographic image canbe obtained.[32]

Treatment and prevention

Medical check-up and screening of all women for presence of CAD and coronary risk factors should begin early, preferably by 40 years of age in all and by 30 yearsof age in those with family history of premature coronary disease, and should be repeated at periodic intervals.

Physical activity[33]

Regular exercise improves insulin sensitivity, decreasesplasma TG levels, and reduces cardiovascular morbidity andmortality. Daily physical activity of 30 min is enough to help reduce and maintain body weight. The activity shouldbe aerobic exercise of moderate intensity like riding a bicycle, jogging, taking a brisk walk, gardening. Physical activity causes successful weight reduction, and along with other therapeutic lifesty lechanges, can reduce the progression of new-onset diabetesby half in patients with metabolic syndrome.

Diet[34]

The Dietary Guidelines describe a healthy diet as one that (a) emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products; (b) includes lean meats, poultry, fish, beans, eggs, and nuts; and (c) has lower amounts of saturated fats, trans fats, cholesterol, salt (sodium), and added sugars. Dietary interventions to lower lipid levels include reductionof saturated fat intake to <10% of the total fat in the diet, reduction of the amount of dietary cholesterol intake, reduction of total fat intake to <30% of the diet, eating more soluble fiber, and maintaining ideal weight.

Management of dyslipidemia[35,36]

Management of dyslipidemia is the cornerstone of therapeutic strategy for CAD risk reduction in women. The five currently available classes of lipid-modifying agents like statins, bile acid sequestrants, nicotinic acid (niacin), fibric acids, and cholesterol absorption inhibitors produce their major effect on one lipoprotein type - LDLbut have lesser effects on the others.For persons with these diagnoses, the LDLgoal is less than 100 mg/dL, irrespective of the presence or absence of CAD. Those who already have CAD require even more aggressive treatment to lower LDL to less than 70 mg/dl (cholesterol <150 mg/dl), specially if they also have highlevels of Lp(a). Therefore, efforts to reduce cholesterol and other CAD risk factors among women appear to be specially crucial.

The statins block the rate-limiting step in cholesterol synthesis and have the most powerful LDL-cholesterol (LDL-c) lowering effects of all lipid-modifying agents. Results of large, randomized CAD prevention trials have consistently confirmed the effectiveness of statin monotherapy in patients with Type-2 diabetes and the metabolic syndrome.[37]

For people with high or very high TG (200 mg/dl or above) as well asthose with a combination of high LDL or a high risk forheart disease and borderline or higher TGs lifestyle changes are generally accompanied by drug therapy. Drug therapies, in this case, include more aggressive LDL lowering drugs or the use of nicotinic acid or a fibrate (gemfibrozil or fenofibrate).

Medical Therapy[38]

All patients with CAD should receive aggressive management of risk factors for progression of atherosclerosis (smoking, hypertension, hyperlipidemia, and diabetes) and pharmacological treatment (antiplatelets, antianginals, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and lipid-lowering drugs).[38] Optimal medical therapy of CAD comprises the combinations of these treatments to reduce future cardiovascular events for all the clinical presentations outlined in the previous section. However, patients may not be able to receive optimal medical therapy if they have allergies to, or adverse effects from, individual medications (e.g., aspirin, beta blockers, or cholesterol-lowering drugs) or the combination of medications. For medical therapy to be optimized, patients should be prescribed appropriate therapy to reach their therapeutic goal. The effectiveness of medical therapy is also affected by how adherent the patient is to the prescribed therapy.

Revascularisation[39]

Coronary revascularization falls broadly into two categories: coronary artery bypass grafting (CABG) and catheter-based percutaneous coronary intervention (PCI). Together, these coronary revascularization techniques are among the most common major medical procedures performed.

CABG is generally preferred for patients with very high CAD burden often described as left main CAD or severe triple-vessel disease with reduced left ventricular function. In contrast, PCI is generally preferred for patients with milder CAD burden described as single- or double-vessel diseasewhen symptoms warrant coronary revascularization, in the light of its lower procedural risk and evidence that PCI reduces angina and myocardial ischemia in this subset of patients.The major advantage of PCI is its relative ease of use and avoidance of general anesthesia, thoracotomy, extracorporeal circulation, central nervous system complications, and prolonged convalescence. Repeat PCI can be performed more easily than repeat bypass surgery, and revascularization can be achieved more quickly in emergency situations. The disadvantages of PCI are early restenosis and the inability to relieve many totally occluded arteries or vessels with extensive atherosclerotic disease. CABG has the advantages of greater durability (graft patency rates exceeding 90% at 10 years with arterial conduits) and more complete revascularization regardless of the morphology of the obstructing atherosclerotic lesion.

STEMI

Treatment for patients with ST-segment elevation is reperfusion therapy (either pharmacological or catheter-based) to restore blood flow promptly in the occluded epicardial infarct-related artery. Pharmacological therapy consists of fibrinolysis or conservative/supportive therapy with facilitated antithrombotic medications.[40] Immediate revascularization with PCI is the preferred strategy when patients have close access to a catheterization facility. Otherwise, fibrinolysis is recommended (in facilities without access) since it also has been shown to improve cardiovascular outcomes.

UA/NSTEMI

Patients with UA/NSTEMI are not candidates for immediate pharmacological reperfusion. The main aims are the immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death or MI). Management is with anti-ischemic therapy, antithrombotic therapy, ongoing risk stratification, and in some cases the use of invasive procedures. In addition to aggressive medical therapy, two treatment pathways have emerged for treating patients without ST-segment elevation.

Angina[41]

The treatment of stable angina has two major purposes. The first is to prevent MI and death and thereby increase the quantity of life. The second is to reduce symptoms of angina and occurrence of ischemia, which should improve the quality of life.All patients with stable angina are candidates for optimal medical therapy and may be candidates for PCI or CABG based on findings from coronary angiography and if symptoms persist despite optimal medical therapy.

Conclusion

CAD in women is becoming more common which is difficult to identify early due to incomplete understanding of the disease mechanisms. The atypical presentations, the unique risk factors, and more frequent normal coronaries on angiography are few of its characteristics. More studies are needed to study these sex-related differences so that optimal gender-specific diagnostic andmanagement strategies can be developed.

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