CORONARY ARTERY DISEASE IN WOMEN

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INTRODUCTION

NICVD is no longer a problem faced by the West alone; on the contrary, it is the developing countries that bear the biggest share of this disease. A staggering 86% of the global burden of CVD is in the developing countries today with 80% of the deaths due to this disease occurring in amongst these countries.[1-2] Numerous studies have reported that Indians have one of the highest rates of CAD in the world[1,3] and the prevalence of CAD in India has more than doubled in the past two decades. Pakistan has a very high disease burden, estimated as 5.09375 million[2] A population based cross-sectional survey showed that 1 in 4 middle aged adults in Pakistan has prevalent CAD. Risks are uniformly high in both, the young and the old women.[4] India and Pakistani women are at higher CV risk than their American counterparts. The data collected from India, where lifestyles of urban communities are similar to Pakistan, also supports the observation of early onset of CHD in Asian women.[5,6,7,8,9,10] The standardized mortality ratio for CAD is much higher for Indian women than men in the United Kingdom[11] and also its risk factors are more prevalent here. It has been suggested that women in the reproductive age bracket are protected from the risk of CHD and in the industrialized world women tend to develop CHD 10 years later than men.[5] In Pakistan, the male to female ratio of patients with MI is 1:3 and the gap is of 5 yrs. Coronary Heart disease has been prevalent amongst women for several decades but it is only now that it is being cautiously scrutinized and described in the medical literature.[12,13,14,2]

The misconception, that CAD is uncommon amongst women (especially the younger groups), and that arteriosclerotic disease is the least important issue to worry about, is vastly prevalent in our society.

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Fig-1 is the truth about the comparison of the prevalence of CAD between both sexes. It clearly shows that the prevalence is equivalent in both groups and in fact, it is higher in females than males in the older age brackets. The belief that women have an innate protection against heart attacks[15] holds true only for premenopausal women. Post menopausal women have loss of the hormone estrogen, which greatly predisposes them to developing CAD. Women are under a false belief of being more vary of diseases like Cancer, Osteoarthritis, Arthritis etc than CAD, whereas heart disease is far ahead of these diseases as the cause of death amongst women.

Fig-1: DISEASES BY AGE AND SEX

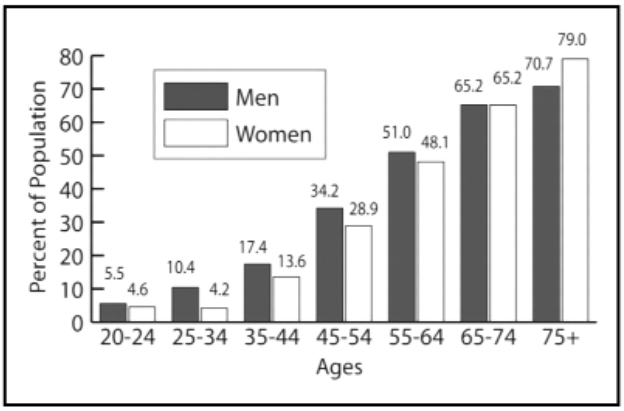
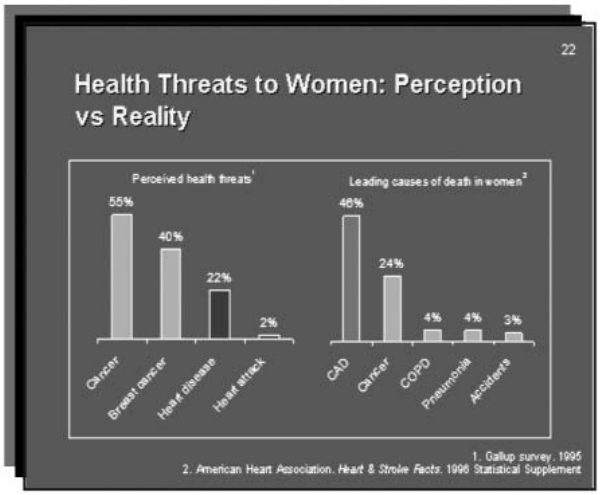


Figure-2 shows that each year more women die from heart disease related causes than from all the Cancer related deaths combined.

Even after the presentation of such clear cut facts, the attitude of the Cardiologists/Physicians has not changed towards tackling women heart disease. It is also important to know that all the research based evidence regarding treatment of CAD has been gathered by experimenting on the male population

Fig-2: PREVALENCE OFCARDIOVASCULAR DEATH



and whether we should implement the same guidelines on women counterparts is an unknown territory.[4,16] A recent initiative of sex-based research has brought forward a rather significant fact that women have different pathogenesis, clinical presentation and complications related to heart diseases as compared to men.[17] Vaccarino et al and Hochman et al have also provided new evidence, based on analysis of large data bases, that there are differences between men and women in the natural history of coronary artery disease that are not related to age.[17] It is, first, important to familiarize with these difference before we can set out to hope for women-based management planning of heart diseases.

(A) GENDER DIFFERENCES IN PATHOPHYSIOLOGY:[18,16,19]

Characteristics of atherosclerosis have been found to be different in women. Blood clot formation is higher in women owing to a higher potential of blood coagulability. In large number of women endothelial dysfunction, small vessel size, and diffuse atherosclerosis has been identified as causes of ischemia without evidence of blockade in the coronary arteries. Atherosclerotic plaque in women is less fibrotic and contains more lipid filled foam cells, implying greater potential for reversibility but also potentially greater vulnerability for plaque rupture and thrombosis. Women have similar magnitude of atherosclerosis, but it looks and functions differently possibly due to estrogen or genetic related reasons. This different pathophysiology results in different clinical presentation of CAD in women.

(B) GENDER DIFFERENCES IN CLINICAL PRESENTATION[16,19]

Clinical diagnosis of angina/chest pain can be very challenging in women. On average they are 10 yrs older than men at the time of presentation. Women present less with typical or classical angina (55% vs. 85%) and more with atypical angina like shortness of breath, fainting, weakness (25% vs.10%) and non-coronary chest pain syndromes (20% vs.5%). These differences should be considered in the evaluation of chest pain and management of acute and chronic ischemic syndrome in women.

(C) GENDER DIFFERENCES IN CORONARY RISK FACTORS[18,11,10,2,20,21,22,5]

15.9% of Pakistani population has at least one risk factor out of four conventional cardiac risk factors. Women have more multiple risk factors (42% vs. 20%), and few women are without traditional risk factors (3.5% vs. 14.3%) as compared to men.[21] Women with ACS ,when compared to men have more prevalence of D/M 61% vs 31%; H/T 75% vs. 43% both of which increase risk of CAD 3-7 fold in women Vs 2-3 fold in men.[21,10] Average elevated total cholesterol and LDL are important risk factor in men but are only weakly associated with CAD in women. Low HDL and high triglycerides are better cause of coronary risk in women than high concentration of LDL. Smoking is more commonly associated with CAD in men, but if women smoke and use oral contraceptives, smoking will significantly increase the risk of CAD. The prevalence of metabolic syndrome, according to the IDF definition and modified ATP III criteria, was 34.8% and 49%, respectively amongst Pakistani women.Thirty percent of women that have metabolic syndrome are affected with CAD. Inclusion of modified waist circumference and specific body mass index (BMI) cut offs for Asians may help predict metabolic syndrome at an early stage. Physical inactivity is more common in Pakistani females (they are kept at home due to our culture) especially in menopausal age and it leads to obesity, HT, and DM which are major cause for CAD.[23] Depression has been found to be an important cause (due to social insecurities) for complications after MI and is seen more in female patients. In a community based study[10] it was found

that compared to PNHS, the prevalence of obesity, H/T, dyslipidemia and WHR were higher in our population[10]. The high prevalence of risk factors in women in Pakistan thus appears to have translated into early and severe CHD in women[5]. The early and severe CHD in Asian women has been variously ascribed to insulin resistance and genetically determined increased lipoprotein Lp(a).[7,24,25] Urbanization and the sedentary lifestyle of Pakistani women may be the most important factor initiating obesity and the clustering of all other risk factors[25]. Novel risk factors. It has been increasingly realized that the traditional risk factors underestimate CHD risk in women. Both CRP and LDL-C show strong linear relationship with cardiac events, with CRP being the stronger predictor. These data suggest that CRP shows promise when added to traditional risk factors for prediction of long term risk.[18]

(D) GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS OF CAD:[16,19,5]

Women present more with USA ??? (37%vs.27%) than NSTEMI, STEMI, and sudden death (62% vs.42%) which are more common presentations in men. There is usually an extended time lapse between the onset of symptoms and seeking medical help amongst women as they tend to try homemade remedies for cure. These delays deny them of early medical treatment and revascularization therapy. Acute coronary syndrome (ACS), a manifestation of CAD is more often clinically silent or misdiagnosed in women than in men (35% vs 28%) because of variation in the presenting symptoms. ECG is less likely to show significant changes in women (37% vs 27%). Cardiac biomarkers like BNP and CRP are better predictors of Ischemic events in women as opposed to the routinely checked CKMB and Troponins, which do not rise to high levels.

(E) GENDER DIFFERENCES IN DIAGNOSTIC PROCEDURES:[16, 19]

Most non-invasive investigations have limitations in women. Resting ECG reveals a higher occurrence of repolarization (ST-T wave) abnormalities in women (32% versus 23%). Exercise Echocardiography and Stress Thallium are more sensitive tests as compared to Exercise Tolerance Test (ETT) in the female population. Women are more likely than men to have normal coronary arteries (26% vs.13%), and less likely to have significant CAD (35% vs.45%). A normal or negative angiogram does not necessarily exclude atherosclerosis or especially in women with risk factors.[16] Women experience ischemia in the absence of significant blockade in heart blood vessels, instead they have increased coronary vascular tone, micro- vascular disease, endothelial dysfunction, and diffuse disease as the possible causes of ischemia / angina. Presenc of these vessel abnormalities is associated with similar cardiovascular complications as in patients with blockade of coronary arteries shown on coronary angiography. So, different cardiovascular diagnostic modalities (routinely not available) should also be used to confirm the diagnosis of ischemia in women.

(F) GENDER DIFFERENCES IN PROVISION OF CARE DURING HOSPITALIZATION:[16,19]

There are no significant differences amongst the two sexes as far as response to treatment benefits is concerned.

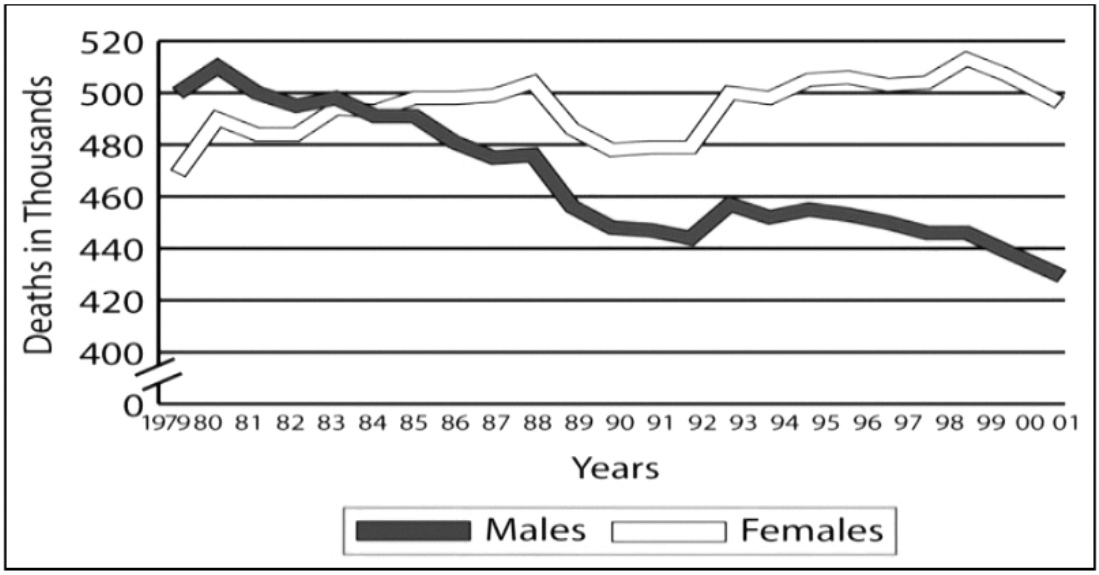
Even then due to gender bias and difficulty in making diagnosis women are less likely to get optimal medical therapy, thrombolytic (88% vs.81%), undergo coronary angiography, and elective and primary angioplasty (14% vs. 25%). It has been seen that women experience more complications from diagnostic angiography and have poorer result after angioplasty. Less women are advised for bypass surgery and when they do undergo the surgery, they are less likely to receive LIMA grafts. Complications after surgery like HF, peri-operative MI, hemorrhage, neurological, and vascular issues are more frequent in women; which may be due to a woman's older age, smaller body size, greater severity of angina, small and more fragile vessels, and greater burden of associated coronary risk factors. As a conclusion, there are different risks /benefits with commonly used therapies given to women for this disease. Most of the disappointing results of CABG in women can be directly related to depression and the societal role (lack of post-operative medical financial support and early involvement in household chores etc) of women.

MORBIDITY AND MORTALITY:[16,19,5]

Figure 3 & 4

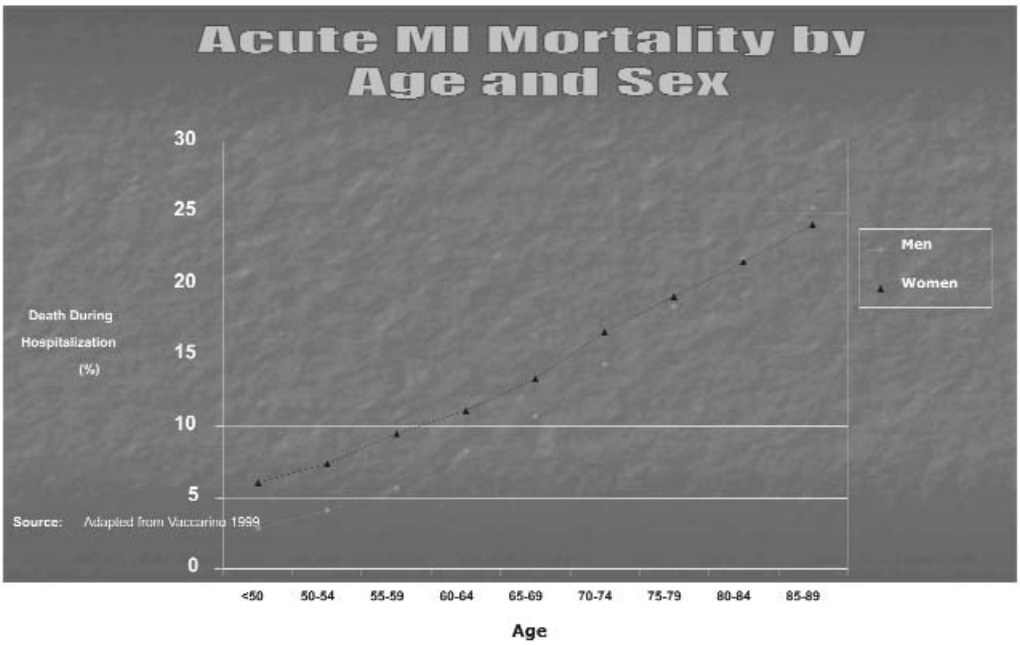
Women have higher rate of severe complications during hospitalization (25% vs.11%). Sixty three percent of women are seen to have sudden death while 42% women (vs.24% men) die within one year of a heart attack. The graph below depicts that the death toll of women has not improved in the last few decades to the same extent as compared to men, despite significant advancements in CAD treatment.

Fig-3: CARDIOVASCULAR DISEASE MORTALITY TRENDS FOR MALES & FEMALES



CARDIOVASCULAR DISEASE PREVENTION IN WOMEN: CURRENT GUIDELINES[26]

Substantial progress has been made in the awareness, and prevention of CVD in women since the first women-specific clinical recommendations for the prevention of CVD were published by the American Heart Association (AHA) in 1999. AHA updated the guidelines for chronic atherosclerotic heart diseases in 2007 and has revised them again, encompassing



prevention of the scope of atherosclerotic thrombotic cardiovascular outcomes in women. The new guidelines are based on trials of CHD prevention.

They recommend a five-steps approach:

Assess and stratify women into high, intermediate, lower and optimal risk categories.

Lifestyle approaches recommended for all women.

Other cardiovascular disease intervention: treatment of hypertension, diabetes, and lipid abnormalities.

Highest priority is for intervention in high risk patients.

Avoid initiating therapies that have been shown to lack benefit, or where risk outweighs benefit.

EVALUATION OF OF CVD RISK:

Evaluate the Medical history, Family history, Pregnancy complication history and symptoms of CVD. Along with that there should be depression screening in women with CVD, physical examination including BP, body mass index, waist size, laboratory test for fasting lipoproteins and glucose, and Framingham risk assessment/score if no CVD or diabetes.

HIGH RISK:

High risk women are those who have > one of the following:

An established coronary artery disease,

Carotid artery stenosis, peripheral arterial disease,

Abdominal aortic aneurysm,

Chronic renal disease (especially ESRD), and

> 20% 10-yr risk for CHD events.

INTERMEDITE RISK/At risk:

Women with Metabolic Syndrome, especially women over the age of 60,

Multiple risk factors,

A single markedly elevated risk factor,

A first degree relative with premature CVD,

Women with subclinical cardiovascular disease (e.g. elevated coronary calcium score),

10-20% 10-yr risk for CHD events.

LOWER RISK:

Women with multiple risk factors, metabolic syndrome, 1 or no risk factor, <10% 10 yr risk of CHD events.

A. LIFESTYLE INTERVENTIONS

It is important for all women regardless of risk status to adopt a healthy lifestyle as early as possible.

i. Smoking

Should be encouraged to stop smoking and avoid environmental tobacco. Women face different barriers for quitting smoking due to their concern about weight gain or it might exacerbate their depression episodes. It is highly recommended that women who use contraceptive pills should never smoke as they have deleterious atherothrombotic effects, when combined .Nicotine replacement therapy and antidepressant can be prescribe to them.

ii. Physical Activity

As I have already discussed 60 and 85 per cent of women are not physically active enough to gain health benefits, they must be encouraged to adopt a minimum of 30 minutes of moderate intensity physical activity such as walking, gardening or cycling, on all days of the week. This task can be achieved even when indoors.

iii. Heart Healthy Diet:

A healthy weight through a balanced diet that includes fruit and vegetables, whole grains, low fat or non fat dairy, legumes, low fat protein, and fish, is an irreplaceable step towards diminishing CVD. Saturated fats should be <10% of calories and <300mg cholesterol. Low fat diet tend to raise triglyceride and lower HDL. The new NCEP guidelines favour a 25% to 35% fat diet ,with only saturated fat restriction(16). Limit trans fatty acid intake (sources are baked goods and fried foods made with partially hydrogenated vegetable oil). It is advisable to substitute animal fats (butter, etc) with soft margarines and monounsaturated oils (olive or canola), or polyunsaturated oils (corn or sunflower), and to limit fried food, fatty meats and salt intake. Ideal weight should be between 18.5 and 24.9 BMI and waist circumference < 35 inches/or 38cm. Weight loss goals should be achieved by reducing 10% of

body weight over six months or 1-2 pounds weight loss/week and reduce calories by 500-1,000 per day and at the same time treat all the components of metabolic syndrome, if present in that patient.[16]

iv. Cardiac Rehablitation:
High risk women with a recent acute CV event, coronary intervention, new onset or chronic angina should participate in a comprehensive risk reduction program, such as cardiac rehabilitation, or a physician-guided home or community based program along with associated risk factor control according to guidelines.

v. Psychosocial Factors:
Women with CVD should be evaluated for depression and should be referred and treated when indicated.

B. MAJOR RISK FACTOR INTERVENTIONS:

i. Hypertension:
Target BP should be < 120/80mmHg. Drug therapy should be started if BP is >140/90 mm Hg and >130/80 in the setting of other co-morbids like diabetes or target-organ damage. Thiazide diuretics should be a part of the drug regimen for most patients, especially in postmenopausal females unless contraindicated or if there are compelling indications for other agents.

ii. Diabetes:
Lifestyle and drugs should be used to achieve the target HbA1C of <7%. Aggressive treatment of all other associated risk factors should be implemented. Regular exercise can also improve glucose control and insulin resistance.

iii. Lipids:
Only diabetic women are candidates for primary prevention. There is no data at present on the efficacy of lipid lowering agents targeted more specifically at altering the HDL-C and triglyceride, which appear more important in women.

a. High Risk Women:
Guidelines same as male patient.

i. Goal LDL < 100mg/dL

ii. Drug therapy in those with LDL-C >130mg/dl after life style modification.

iii. Drug therapy in those with LDL-C>190mg /dl regardless of other risk factors and advise to maintain HbA1c<7% in diabetics.

iv. Therapy with niacin or fibrates when HDL-C is low or non-HDL-C is elevated (after LDL-C goal reached)

v. Non HDL <130mg/dl

b. Intermediate Risk Women
Target LDL <100 mg/dl

c. Lower Risk Women

i. Drug therapy if LDL ≥ 190 mg/dL.

ii. Drug with multiple risk factors and LDL-C >160mg/dl

C. PREVENTIVE DRUG INTERVENTIONS FOR WOMEN WITH CVD

a. Aspirin

- Aspirin or Clopidogril can be used in high risk women or for secondary prevention. Aspirin therapy can be useful in women > 65 y of age (81mg daily or 100 mg every other day) If the BP is controlled then the benefit for ischemic stroke and MI prevention is likely to outweigh risk of bleeding and hemorrhagic stroke. Hence ASA may be a reasonable choice for women <65y of age for ischemic stroke prevention
- Aspirin 75-325mg should be used in women with chronic or paroxysmal Atrial fibrillation with contraindication to Warfarin or at low risk of stroke (<1%/y or CHADS2 score of <2)
- Aspirin therapy (75-325mg) is reasonable in women with diabetes, unless contraindicated.

b. Beta-Blockers:
It should be used after myocardial infarction, ACS, or LV dysfunction.

c. Angiotensin-Converting Enzyme Inhibitors:
Should be used after MI or with clinical CHF, LV dysfunction (EF<40%) and diabetes. ARBs can be added if there is intolerance of ACE-inhibitors.

d. Aldosterone blockade:
Should be used after MI in symptomatic women with LVEF<40%.

e. Reproductive Age Women and CHD

Over 10,000 reproductive age women suffer MI each year. All women of reproductive age prescribed with drug therapy should be counseled about preconception planning, as many recommended drugs are contraindicated during pregnancy. Reproductive age women with CHD who are pregnant or planning pregnancy should be cared for by Obstetrics and Cardiovascular team approach.

D. INTERVENTIONS THAT ARE NOT USEFUL / EFFECTIVE AND MAY BE HARMFUL FOR THE PREVENTION OF HEART DISEASE

Hormonal Therapy:

Several observational studies demonstrated the efficacy of HRT in decreasing the incidence of coronary events along with curbing the symptoms of menopause. However, its role in CVD prevention still remains unclear and without substantial evidence. The Women's Health Initiative (WHI) trial demonstrated an increased risk of breast cancer and cardiovascular events (AMI, stroke, pulmonary embolism and deep venous thrombosis) and a significant reduction in risk of colorectal cancer and, eventually, hip fracture (37 and 33%, respectively) among women on HRT. Despite some of these favourable effects, it is not wise to prescribe HRT for primary or secondary prevention of CVD in premenopausal women.[16] It makes good sense for women taking OC to have their lipoprotein and glucose levels checked at least once after starting to continue managing heart disease risk factors aggressively.

a. Antioxident supplements:

No cardiovascular benefits in randomized trials of primary and secondary prevention.

b. Folic Acid Supplementations (Class-11b):

May be considered in high risk women if a higher than normal level of homocysteine has been detected.

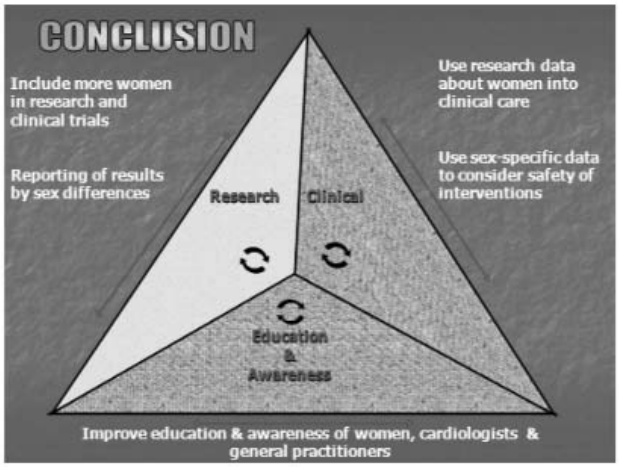
c. OMEGA-3 Fatty Acids (Class-11b):

Can be added as an adjunct to diet. Omega-3 fatty acid in the form of fish or capsules, for the primary and secondary prevention of hypercholestrollaemia and/ hypertriglycerdeamia supplements may be considered in high risks women.

CREATING CHANGE

There is a tremendous need for action in our population regarding knowledge and public understanding of CAD so that this issue may be effectively dealt with. At a time when health information is easily accessible and widely spread, many women are still not aware that CAD is infact one of the most important quencher of women's lives. Adoption and application of new knowledge regarding sex differences will hopefully lead to improved results in women medicine.

Some, yet important, positive steps have been seen in the face of published articles, in the press (read by common man) as well as in medical journals, about the importance of cardiovascular health in women.[16] The "Go Red for Women" Campaign, launched by WHO (in 2004) and adopted by the Pakistan Cardiac Society in 2007, to bring awareness about Coronary Artery Disease (CAD) in women is now reaching an epidemic proportion.[4,23] We are on the right track to reach our goal, however, this is just the beginning and there are miles to our destination. In this regard, the basic skill of practitioner must be joined with those of the epidemiologist, clinical trialist, and clinical and basics researchers to carry this forward.



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