

Coronary Artery Disease in Women

Enas A Enas, A Senthilkumar, Vijaya Juturu, Rajeev Gupta

*Coronary Artery Disease in Indians Research, Lisle, USA and
Mahatma Gandhi National Institute of Medical Sciences, Jaipur, India*

Women now outlive men by 10 years, thanks to the dramatic (>99%) decline in obstetrical death rate over the past 100 years. Women represent 60% of those over the age of 65 years in the United States (US) and more women than men have died of cardiovascular disease (CVD) since 1984.¹ There has been an explosive increase in the knowledge of the natural history of coronary artery disease (CAD) in women in the past decade. This is due to a combination of greater participation of women in research studies, improved medical technology, and perhaps political pressure. Among women, the lifetime risk of death from CAD is more than 10-fold greater than that from breast cancer.² It is estimated that 31% of women will die from CAD; yet, about 70% of university educated women consider their risk of CAD to be <1%. They worry profoundly about breast cancer, although the risk of death from breast cancer is <3%. This lack of concern for CAD by women and perhaps their physicians could explain why the decline of CAD in women in western countries has been only half that of men. The excess of CAD among overseas Indians has been similar or greater in women than in men,³ and offers a broad “window to the world” for the impending epidemic of CAD among Indian women. In this article, the term “Indian” refers not only to people of Indian origin but all those originating from the entire Indian subcontinent.

This review discusses the progress in understanding the major risk factors leading to the high rates of CAD in women, especially in India. The potential role of genetic susceptibility to CAD mediated by elevated lipoprotein (a) [Lp(a)] levels and its synergistic adverse effects with both conventional and emerging risk factors are highlighted. Important differences in the presentation, diagnosis and treatment of CAD in women, and the unique role of hormone replacement therapy (HRT) are addressed. Finally, we offer recommendations to both Indian women and their physicians in reducing the morbidity and mortality from CAD.

Correspondence: Dr Enas A Enas, *Coronary Artery Disease in Indians Research, 1935 Green Trails Dr, Lisle, IL 60523 USA*
e-mail: cadiusa@msn.com

Magnitude of CAD in Indian Women

CAD rates in India: Since 1960, life expectancy in India has increased by 20 years to 61 years of age.⁴ From 1960 to 1995, the prevalence of CAD in adults increased from 3% to 10% in urban Indians and from 2% to 4% in rural Indians, with women having rates similar to men.⁵ Although the prevalence of CAD in rural India is half that of urban India, this is still two-fold higher than the overall CAD rates in the US and several-fold higher than in rural China.⁶ In 1990, there were 783 000 deaths due to CAD in India and this is projected to double by the year 2015, primarily due to affluence and urbanization. Young Indians with CAD have extensive coronary atherosclerosis, with even premenopausal women having multivessel disease, a pattern rarely seen in the West.

CAD rates among overseas Indians: Although more women than men die annually from CAD, the age-adjusted standardized mortality rate (SMR) for CAD among women is about one-third that of men all over the world. This is due to a higher age (average 10 years) in women at the time of death. The excess of mortality due to CAD among overseas Indians is equal or greater in women than men. This is particularly noteworthy since smoking is rare among Indian women. In the US, Indian women have the highest CAD mortality—30% higher than Whites and 325% higher than the Chinese.⁷

Excess CAD morbidity and mortality in women:

Women have a poorer prognosis and a more severe outcome than men after myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG). Women are more likely than men to die after a first MI, and for survivors, there is a higher risk of recurrent MI, heart failure, or death.⁸ In the Framingham Heart Study (FHS), the one-year mortality following an MI was 44% in women versus 27% in men.⁹ The overall short-term and long-term CAD mortality following an MI are about 40% higher in women after adjustment for age and other risk factors. The excess in-hospital CAD mortality in women compared to men almost balances their lower prehospital mortality.¹⁰ Despite their

excess risk, women are only half as likely as men to receive aspirin, betablockers or thrombolytic therapy, or to be referred for coronary angiogram or revascularization procedures.¹¹ This difference is rapidly disappearing in the US but not all over the world. Recently, Vaccarino et al.¹² found that mortality from MI in women <50 years of age was double that of men and the excess mortality in women is limited to <60 years of age. This is in sharp contrast to a report from India showing lower rates of morbidity and mortality in young women and deserves greater scientific scrutiny.

Presentation of CAD: Although women are more likely than men to present with angina as the initial complaint, the reliability of typical angina as a sign of CAD is poor. In the FHS, only 17% of women with typical angina developed an MI compared with 44% of men.¹³ In the Coronary Artery Surgery Study (CASS), only 50% of women with typical angina had significant CAD compared with 83% of men. Whether this discrepancy is due to over-reporting of chest pain by women or under-reporting by men is unclear. Women having an MI are more likely to present with atypical chest pain (midback pain) and atypical symptoms (indigestion, nausea, vomiting and dyspnea).¹⁴ They present to the hospital significantly later than men, which may decrease the benefit of reperfusion therapy.

Sudden death: More than half of sudden deaths occur within six hours of the onset of symptoms. Early diagnosis is important, since two-thirds of women who experience sudden death have no previous symptoms of CAD, compared with about half of men.¹⁵ The risk factors and mechanisms of sudden coronary death differ between older and younger women. Older women who die of CAD often have dyslipidemia, with severe coronary narrowing and plaque ruptures. Young women who die of CAD are often smokers with plaque erosions and little coronary narrowing. However, most young Indian women with CAD have advanced CAD resembling that in older women.¹⁶

Coronary Risk Factors

Women, in comparison with men, tend to have a better risk factor profile at younger ages, whereas the opposite is true at older ages. Although most risk factors for CAD are similar in men and women, gender differences have been documented, particularly for diabetes, central obesity and dyslipidemia. Among Indian women, the presence of hypertension, diabetes, low levels of high density lipoprotein (HDL) and high levels of total cholesterol (TC), triglycerides

(TG), low density lipoprotein (LDL), and Lp(a) are correlated with CAD.¹⁷ Compared with Whites, Indian men and women have a lower prevalence of hypertension, hypercholesterolemia, obesity and smoking, but a higher prevalence of high TG, low HDL, glucose intolerance and central obesity. The prevalence of most risk factors is lower in rural than in urban India with the exception of smoking/tobacco use.¹⁸ The higher rates of CAD in urban areas despite a low rate of tobacco use (Tobacco Paradox) underscore the critical importance of factors associated with urbanization.

Asian Indian ethnicity: At a given level of risk factors, compared to Americans, the CAD risk is 50% lower among southern Europeans but 50% higher among northern Europeans.¹⁹ The risk of CAD among Indians is even greater than in northern Europeans at any given level and/or combination of conventional risk factors—at least double that of Americans and several-fold higher than other Asians.²⁰ At any given level of TC the CAD risk varies >5-fold depending on ethnicity and level of other risk factors.²¹ Indian ethnicity has now been demonstrated to be a risk factor by itself.²²

Family history: Among women, a history of an MI or sudden death before the age of 55 in a sister is more strongly associated with risk of MI than that in a brother or parent. A family history of premature CAD in a sister is associated with a 12-fold higher risk versus 6-fold for a brother and 3-fold for a parent.²³ Since choosing one's parents or siblings is not an option, this topic will not be discussed further except that women with a family history of premature CAD, especially in a sister, should follow a course of action similar to the one recommended for those who had survived an MI or had coronary revascularization at a young age.

Age: Compared with the age group 34–44, CAD mortality among women increases 40-fold by the age of 80, when its incidence become identical in men and women. Women are about 10 years older than men at first manifestation of CAD, although they have a similar plaque burden.²⁴ Women lose this 10-year advantage if they smoke, have diabetes, or had a premature menopause. The postmenopausal increase in the risk of CAD is related to a higher incidence of hypertension, diabetes, dyslipidemia and obesity. The steady increase in CAD mortality with age is in sharp contrast to that of breast cancer, which peaks between the ages of 40 and 50 years and declines steadily thereafter.

Height: Height is inversely associated with CAD in women as it is in men. In a large study involving about 2000 women, short women (<59 inches) had a 3-fold higher risk

of CAD than taller women (>69 inches), after adjusting for age, weight, educational status, religion and other factors.²⁵

Generalized obesity: Obesity is associated with increased risk of hypertension, diabetes, dyslipidemia and CAD. Body Mass Index (BMI), which is defined as the weight in kilograms divided by height in squared meters (kg/m^2) is now accepted as the single best measure of obesity.²⁶ In the 16-year data from the Nurses' Health Study (NHS), CAD mortality was 4-fold lower in lean ($\text{BMI} < 21$) than in obese women.²⁷ For Asians, the optimum BMI is < 23 , whereas > 23 is considered overweight and > 25 obese.²⁸ Thus the BMI cut-off points for overweight is 2 units, and obesity 5 units lower in Asians than in Whites.

Central obesity: The distribution of fat is of equal or greater importance as the total amount of fat. Marked adverse metabolic consequences are seen with central obesity (android or apple-type) but rarely with gluteo-femoral obesity (gynoid or pear-type). The waist-to-hip ratio (WHR) has been traditionally used to measure central obesity. This is a better marker for CAD death than BMI in women under 50 years of age. Because the excess fat is usually concentrated in the hip in women and the waist in men, the optimum WHR is lower in women (< 0.75) than in men (< 0.95).²⁹

Recently, waist circumference has been found to be a simple and better marker of central obesity than WHR. In women, the optimum waist circumference is 10 cm lower— < 80 cm in women and < 90 cm in men. These values are about 8–10 cm lower than that recommended for Whites and underscore the need for instituting a weight management program at much lower BMI and waist circumference in Indian men and women. At a given level of WHR or waist circumference, CAD rates are identical in men and women. It is plausible that sex differences in central obesity are the key to the gender gap in CAD.

The recognition of the significance of central obesity should not divert attention from the metabolic consequences of noncentrally obese individuals who need to reduce weight. Among Indians, as in other populations, both BMI and WHR are related to CAD risk factors in a graded manner; the maximum risk occurs in apple-shaped overweight and minimum in pear-shaped lean individuals.³⁰

Adult weight gain and weight reduction: Atherogenic risk factor clustering is common in both sexes and worsens with weight gain. Age-related increase in weight and waist circumference is greater in women than in men and is closely related with decrease in physical activity. A weight

gain of even 7–11 kg after the age of 18 years has substantial health consequences, with a doubling of risk for diabetes and CAD in women.²⁷ Middle-aged women who lose ≥ 5 kg of weight have a significantly reduced risk for diabetes. The recommended weight reduction is about 0.5 kg per week and this requires a negative caloric balance of 3500 calories equal to walking 56 km per week.

Physical activity: Physically active women have a 50% lower risk of CAD than sedentary women.³¹ Increased physical activity along with diet can prevent a rise in LDL and weight gain, especially around the waist. Daily walking for 45–60 minutes is necessary to prevent weight gain in most women. However, even walking 2 km per week produces a favorable risk factor profile, especially fibrinogen and insulin levels, and reduces the CAD risk. Home physical activity is positively related to favorable lipoprotein levels, with those engaging in heavy home physical activity having higher HDL levels. Other benefits of exercise include reduced risk of breast cancer (relative risk 0.28).

Socioeconomic status (SES) and psychosocial factors: CAD has now become a disease of the poor in rich countries and of the rich in poor countries. Women with less than a high school education have a 30%–50% higher CAD mortality than those with higher education. Depression, high hostility, low social support and low education level are associated with CAD, after controlling for adverse health behaviors. Indians with low literacy have a higher prevalence of CAD and risk factors such as smoking and hypertension. However, differences in SES failed to explain the excess burden of CAD among Indians in the UK. Despite having a lower level of TC, Indians had a 3- to 4-fold higher odds ratio for a high-risk lipid profile, after controlling for SES, age and sex.³² The impact of psychosocial and behavioral factors on CAD in Indian women requires further investigation.

Paradox of healthy lifestyle and shorter lifespan in women physicians: Women physicians in the US report having generally good health habits and exceed all examined national goals for personal screening practices and other personal health behaviors. Women physicians' behaviors may provide useful standards for other women. Ironically, women physicians die an average of 10 years earlier than their male counterparts, the opposite of what happens in the general population. The suicide rate among female physicians is higher than that for male physicians and four times higher than the age-matched female population and may partially explain their lower life span despite a healthy lifestyle.

Tobacco abuse: Due to its anti-estrogenic effects, smoking quadruples the risk of MI in young premenopausal women. It is a stronger risk factor in women than in men. Over 50% of MI in middle-aged women in the US is attributable to cigarette smoking. The risk of CAD begins to decline within months of cessation of smoking and disappears within 3–5 years. The smoking cessation rates have declined more slowly in women in the US, especially younger ones than in men and parallel slower rates of decline of CAD in women. The overall rate of smoking is low among Indian women, particularly in urban areas.

Passive smoking: Although only 8% of the women in Asian countries smoke, >60% of the men are smokers.³³ Therefore, vast numbers of women and children are exposed to environmental tobacco smoke (ETS), which increases platelet activity, accelerates atherosclerosis, reduces exercise tolerance, and increases the risk of both fatal and nonfatal cardiac events. Urgent public health measures are needed to reduce the dangers of both active and passive smoking in India.

Hypertension: Hypertension confers a 4-fold risk of CAD in women versus a 3-fold one in men. Hypertension tends to be more common in women than in men after 45 years of age (White women 60% and Black women 79%). The systolic blood pressure (BP) continues to increase disproportionately in women until the age of 80. Hypertension is closely correlated with obesity and is 6-fold higher in women with a BMI >30 versus BMI <20. Conversely, a weight reduction of 9 kg can lower systolic BP by 6 mmHg and diastolic BP by 3 mmHg in hypertensive patients.³⁴

Insulin resistance syndrome or Syndrome X: This is a precursor of diabetes and a common pathogenic mechanism for the development of CAD. This syndrome is particularly common among Indians and consists of hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, prothrombotic state, central obesity and hypertension. This is different from the cardiac syndrome X (angina with abnormal treadmill test and normal coronary angiogram), which is also more prevalent in women. It is unclear if the cardiac risk in this syndrome exceeds that of the constituent risk factors.³⁵

Diabetes mellitus: In the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), diabetes is regarded as a CAD risk equivalent.³⁶ Diabetes is a stronger risk factor for CAD in women than in men, with a 3- to 7-fold higher CAD incidence and mortality compared to a 2- to 3-fold higher risk in men.³⁷ Diabetes increases the risk of

heart failure by 8-fold in women compared to 4-fold in men; diabetes eliminates the protective effects of estrogens and removes the normal sex difference in the prevalence of CAD.³⁸ Premenopausal women with diabetes face a similar risk of developing CAD as nondiabetic men of the same age.³⁹ Following an MI, diabetic women have double the rate of recurrence and shorter survival than men.

Diabetic dyslipidemia: Approximately 80% of deaths in diabetic patients are attributable to CVD, which in turn is highly correlated with dyslipidemia.⁴⁰ Diabetic dyslipidemia consists of elevated TG, low HDL, and an increased proportion of small dense LDL. Recently, the NCEP ATP III has also recommended an LDL goal of <100 mg/dl in diabetic patients, irrespective of the presence or absence of CAD.³⁶ Diabetic women with HDL ≤50 mg/dl and TG ≥100 mg/dl have high CAD mortality and should be treated aggressively. Treatment of dyslipidemia with statins in patients with both impaired fasting glucose and diabetes is highly cost-effective.

Crucial Role of Dyslipidemia

Total cholesterol (TC): Total cholesterol levels in women compared to men are about 10 mg/dl lower before the age of 45 and 10 mg/dl higher after the age of 65. A 20% difference in TC level is associated with a 50%–60% difference in CAD risk over a lifetime.⁴¹ The optimum TC level appears to be <160 mg/dl.

LDL: The LDL fraction of TC is a strong predictor of CAD mortality in women as well as in men. Unlike in men whose LDL levels plateau at the age of 50 years, the LDL levels in women increase steadily by an average of 2 mg/dl/year between the ages of 40 and 60 (total of 40 mg/dl).⁴² The optimum LDL level is <100 mg/dl.³⁶

HDL: Low HDL is an important risk factor even if TC and TG levels are normal. It is a stronger predictor of CAD in women than in men, especially after the age of 65; indeed, the protective effect of HDL is twice as important as the atherogenic effect of LDL. High density lipoprotein levels are about 10 mg/dl higher in premenopausal women than in men. Among women, the HDL levels vary markedly depending on the ethnicity, with Indian women having the lowest levels. The HDL level among Indian women (45 mg/dl) is about 10 mg/dl lower than in Whites (55 mg/dl) and 20 mg/dl lower than in Blacks, the Chinese and Japanese (65 mg/dl). These high levels of HDL among Black, Chinese and Japanese women also parallel their low rates of CAD,⁶ whereas the low levels of HDL in Indian women parallel their high rates of CAD.⁴³

The NCEP ATP III has classified HDL <40 mg/dl as low HDL and >60 mg/dl as high HDL.³⁶ In India, 32% of urban and 18% of rural women have HDL levels <40 mg/dl. Many experts consider HDL <50 mg/dl to be low in women. In the Coronary Artery Disease in Indians (CADI) study,⁴⁴ 70% of Indian women had HDL levels <50 mg/dl. If the level is <35 mg/dl, it confers an 8-fold higher CAD risk than an HDL of >75 mg/dl in women.⁴⁵

Total cholesterol/HDL (TC/HDL) ratio: This ratio is now widely recognized as the single best predictor of CAD. At any given level of TC/HDL ratio, the CAD risk is virtually identical in men and women.⁹ Indian women worldwide have a high TC/HDL ratio by virtue of low HDL, even when TC levels are not elevated.⁴⁶ The optimum TC/HDL ratio is 3 and the average ratio is 4. A TC/HDL ratio >5 appears to be a strong predictor of CAD, and is observed in 25% of industrial and 32% of urban female populations in India.¹⁸

Triglycerides: A high TG level is a stronger predictor of CAD in women than in men. An increase in TG level of 90 mg/dl increases the CAD risk by 75% in women versus 30% in men.⁴⁷ A high TG level was significantly associated with cardiac and total mortality in a 20-year follow-up of Swedish women.⁴⁸ Conversely, low TG (<97 mg/dl) and high HDL (>57 mg/dl) is associated with very low risk of CAD,⁴⁹ but is uncommon among Indians. A low level of HDL often accompanies a high TG. The optimum TG level is <150 mg/dl.

Lipid triad: The combination of high TG, low HDL and high small dense LDL is called the lipid triad. The TG level is the principal determinant of small dense LDL, which in turn is the link between cholesterol and TG metabolism.⁵⁰ The predominant form of LDL is small and dense when HDL is <40 mg/dl and TG >100 mg/dl.⁵¹ Recently, a TG/HDL ratio of >3 was found to be a simple, accurate and inexpensive predictor of small dense LDL.⁵² Individuals with small dense LDL have a 3-fold higher risk of CAD, which increases to 20-fold when apolipoprotein B (Apo B) and insulin levels are also raised.⁵³ All these abnormalities are common among Indian men and women, rendering them highly susceptible to CAD.⁵⁴

Lipoprotein(a): An elevated level of Lp(a) is a powerful risk factor for the presence and severity of premature CAD in women as well as in men. Since its pathological effects begin in infancy, Lp(a) is a stronger determinant of CAD in premenopausal than in postmenopausal women. The pathogenicity of Lp(a) is markedly influenced by other risk factors, especially low HDL, a high TC/HDL ratio, and high

homocysteine levels. For example, high levels of Lp(a) increase the risk of CAD by a factor of 5 when associated with hypertension, by a factor of 7 with high TC/HDL ratio, by a factor of 8 with low HDL and by a factor of 9 with high homocysteine. The combination of all four of the above increases the risk of CAD by a factor of 122.⁵⁵ Lipoprotein(a) level was a powerful predictor of mortality in the 4S study.⁵⁶

Lipoprotein(a) appears to be a stronger risk factor than diabetes in young women. Indian women in the US have a higher CVD risk than their American counterparts, by virtue of central obesity, high Lp(a) levels, and an atherogenic lipid profile. Although Lp(a) levels are largely genetically determined, there is a 10% increase in Lp(a) levels in postmenopausal women. Hormone replacement therapy (HRT) reduces Lp(a) levels by an average of 20% (up to 50% in women with high Lp(a) levels). The role of Lp(a) among Indians has been reviewed recently.⁵⁷

Homocysteine: An elevated homocysteine level is a risk factor for MI, especially among young women. After adjusting for other CVD risk factors, women with homocysteine levels ≥ 15.6 $\mu\text{mol/L}$ have twice the risk of MI as women with homocysteine levels <10 $\mu\text{mol/L}$. The most common cause of elevated homocysteine is low folate levels, though many patients also have low levels of vitamins B₆ and B₁₂.⁵⁸ Prolonged cooking of vegetables, a common practice in India, can result in the destruction of up to 90% of the B group of vitamins.⁵⁹ The optimum homocysteine level is <10 $\mu\text{mol/L}$. The combination of high Lp(a) and high homocysteine levels is very common among Indians and carries a 32-fold increased risk of CAD.⁵⁵ The multiplicative effects of the emerging and conventional risk factors best explain the excess burden of CAD among Indian men and women.

Diagnostic Testing and Coronary Revascularization

Noninvasive diagnostic testing: Although women with resting ischemic electrocardiographic findings have an increased risk for CAD, false-positive stress tests may be seen in as high as 50% of women with chest pain.⁶⁰ This is particularly true in those on HRT, which produces ST segment depression similar to a digitalis-like effect. Therefore, the accuracy of stress testing depends on the Bayesian principles.

Stress imaging, including thallium myocardial perfusion imaging, has lower sensitivity and specificity in women than in men, possibly due to smaller left ventricular chamber size, hormonal milieu, and autonomic imbalance.^{60,61} Estimation of coronary calcification by electron beam computerized tomography has a low sensitivity among premenopausal

women and its role in detection of CAD is currently evolving. Stress echocardiography appears to be superior in identifying women who require further expensive diagnostic and therapeutic interventions.

Coronary angiography: Of the 323 women enrolled in the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study, 57% had no significant CAD (34% not detectable, 23% minimal stenosis) versus 43% with significant CAD (stenosis >50%) on coronary angiogram.⁶² The contemporary common finding of "no CAD" and "extensive CAD" at coronary angiography among symptomatic women with similar presentations is similar to the CASS data reported 20 years earlier.⁶³ These findings underscore the need for better use of noninvasive tests to identify women who are candidates for invasive procedures.

PTCA: Women who are hospitalized for CAD undergo fewer invasive procedures than men. Whether this difference represents overtreatment of men or undertreatment of women or both remains to be determined.⁶⁴ Although women have excellent long-term prognosis after successful PTCA and stent insertion, similar to that observed in men,⁶⁵ the procedural morbidity and mortality are 3-fold higher in women,⁶⁶ which may be due to severity of their underlying disease rather than gender alone.⁶⁷ Recent evidence suggests that the gender bias against aggressive intervention and treatment of CAD in women is disappearing in the West.⁶⁸

CABG: Women in general are more severely ill than men and have double the mortality following CABG.⁶⁹ People with small body size have small coronary arteries but women have smaller coronary arteries than men despite controlling for differences in body size.⁷⁰ Small coronary artery diameter is associated with substantially increased risk of in-hospital mortality following CABG. Thus, smaller coronary artery diameter is one explanation for the higher perioperative mortality and poorer long-term success with CABG in women.⁷¹ Women have less graft patency and symptom relief and higher reoperations within the initial five years following CABG. A high TG level is particularly dangerous in women who undergo CABG.⁷² Aggressive lipid-lowering therapy can stabilize the vulnerable plaque and thus provide a more stable milieu for CABG to avoid the need for repeats and "3-peats".⁷³ A strategy of delayed revascularization with optimum medical therapy is advisable. Women have higher risk profiles and are older; yet, the unadjusted 5-year mortality rates in women and men undergoing CABG and PTCA are similar. This would

suggest that the gender differences in mortality related to CAD do not exist, or may even be lower in women, after adjusting for age, risk factors and interventions.⁷⁴

Preventive and Therapeutic Implications

Asymptomatic progression of CAD: Atherosclerosis is a disease that manifests clinical symptoms only late in its development. Coronary artery disease is not a categorical event but rather a continuum of a progressive process.⁷⁵ Sudden cardiac death may be the first symptom and such patients obviously cannot benefit from secondary prevention. Furthermore, women fare worse following an MI than men; therefore primary prevention is even more important in women.

Comprehensive guide to risk reduction in women:

The American Heart Association recommendations can be modified to suit Indian conditions.⁷⁶ Caloric intake should be balanced to caloric expenditure to achieve and maintain optimum BMI. Regular exercise is mandatory for both men and women. Women who have gained 5 kg of weight or 5 cm of waist should be advised by physicians to make gradual but permanent adjustments in physical activity and eating patterns. The essential ingredients and goals for risk reduction in women are given in Table 1.⁷⁷

Undertreatment of dyslipidemia in women: About 50% of women >55 years of age qualify for drug treatment under NCEP ATP III guidelines in the US.³⁶ In the Heart and Estrogen/Progestin Replacement Study (HERS), only 9% met the LDL goal of <100 mg/dl.⁷⁸ Another study found only 12% of women achieved the LDL goal compared to 31% of men. This underscores the need for a more aggressive approach to the treatment of dyslipidemia in women.

Statins in the prevention and treatment of CAD: Most physicians do not wait for the development of stroke to treat hypertension, or coma to treat diabetes. The benefit of dyslipidemia treatment with statins is several-fold greater than treatment of hypertension or diabetes. There is no justification to delay or deny the use of statins to treat dyslipidemia in asymptomatic women until a cardiac catastrophe. Development of angina should be considered a medical failure rather than the first indication for mechanical intervention.

Landmark trials and benefits of statins: Convincing evidence now exists about the substantial reduction in CAD morbidity and mortality due to lowering of lipid levels with statins in women. In the Cholesterol And Recurrent Events (CARE) trial, the reduction in major acute coronary events

Table 1. Guide to CAD risk reduction for women

<i>Lifestyle factors</i>	<i>Goal(s)</i>
Cigarette smoking	Complete cessation Avoid passive smoking
Physical activity	Accumulate ≥ 30 min of moderate-intensity physical activity daily Women who have had recent cardiovascular events or procedures should participate in cardiac rehabilitation, a physician-guided home exercise program, or a comprehensive secondary prevention program
Nutrition	Low SAFA diet (<7% energy and <200 mg/dl cholesterol) High MUFA diet (up to 20% energy) for those with high TG and low HDL Nuts up to 30 g per day Total dietary fiber intake of 25–30 g/day Five or more servings of fruits and vegetables per day Avoid prolonged cooking of vegetables Limit salt intake to 6 g/day (lower in women with high blood pressure)
Weight management	Achieve and maintain desirable weight (BMI <23 kg/m ²) Desirable waist circumference <80 cm
Psychosocial factors	Positive adaptation to stressful situations Improved quality of life Maintain or establish social connections
<i>Risk factors</i>	<i>Goal(s)</i>
Blood pressure (BP)	Achieve and maintain BP <140/90 mmHg (optimal <120/80 mmHg)
Lipids, lipoproteins	LDL <100 mg/dl; TC <160 mg/dl; TG <150 mg/dl; HDL >50 mg/dl; Lp(a) <20 mg/dl
Diabetes	Maintain blood glucose: preprandial 80–120 mg/dl, bedtime 100–140 mg/dl Maintain HbA1c <7% BP <130/85 mmHg
<i>Medications</i>	<i>Goal(s)</i>
HRT	Initiation or continuation of HRT in women for whom the potential benefits may exceed the risks (Lp(a) >20 mg/dl; HDL <50 mg/dl)
Oral contraceptives	Minimize risk of adverse cardiovascular effects while preventing pregnancy. Use the lowest effective dose of estrogen/progestin
Antiplatelet agents/ anticoagulants	Prevention of clinical thrombotic and embolic events in women with established CAD. Primary prevention studies are in progress
Beta-blockers	To reduce the reinfarction rate, incidence of sudden death, and overall mortality in women after MI
ACE inhibitors	To reduce the morbidity and mortality among MI survivors and patients with or without LV dysfunction

SAFA: saturated fatty acid; MUFA: monounsaturated fatty acid; HRT: hormone replacement therapy (Adapted from Mosca L, 1999⁷⁷)

(MACE) in women (46%) was more than double that in men (20%).⁷⁹ Other statin studies with substantial enrolment of women have also shown an impressive risk reduction (RR); 4S⁸⁰ (827 women, RR 37%), LIPID⁸¹ (1508 women, RR 15%), and AFCAPS/TexCAPS⁸² (997 women, RR 46%).⁸³

Statins reduce clinical coronary events by stabilizing the vulnerable plaques, disruption of which results in MACE.⁸⁴ In women this disruption is usually related to plaque erosion, in contrast to plaque rupture in men.⁸⁵ Other differences in CAD between men and women are shown in Table 2. Recently, statins have been shown to increase bone

density and decrease fractures, dementia and stroke, all of which provide additional benefits in women.^{86,87} Preliminary data also indicate a reduced risk of breast cancer among statin users.

Lipoprotein goals among Indian women: NCEP ATP III recommends levels of LDL <100 mg/dl, TG <150 mg/dl, HDL >40 mg/dl as optimum.³⁶ These levels must be achieved in women with or at high risk of CAD. Since the overall risk of MACE in Indians without CAD is similar to Whites with CAD, all Indians should strive to achieve and maintain these optimum levels. This is especially true for

Table 2. Cardinal differences in CAD between men and women

	Men	Women
<i>Manifestation of CAD</i>		
Age at first clinical manifestation	—	10 years later
Age at first MI	—	20 years later
Age at CAD death	—	8 years later
Silent MI	+	++
CAD presenting as unstable angina	++	+++
Acute MI presenting with atypical angina	+	++
Acute MI presenting as atypical symptoms	+	++
Sudden death	++	+++
Sudden death without prior symptoms	++	+++
CAD presenting as acute MI	+++	++
Plaque rupture as the mechanism of acute MI	+++	+
Plaque erosion as the mechanism of acute MI	+	+++
<i>Relative risk of CAD with risk factors</i>		
High LDL	+++	++
Low HDL	+++	++++
High Lp(a)	++	++++
High TG	++	+++
Diabetes	++	++++
Severity of risk factors at the time of acute MI	++	+++
Number of risk factors at the time of acute MI	++	+++
<i>Diagnostic testing</i>		
Sensitivity and specificity for exercise treadmill test	+++	++
Sensitivity and specificity with thallium treadmill test	+++	++
Sensitivity and specificity with stress echocardiography	+++	+++
<i>Complications and prognosis</i>		
Good prognosis with typical angina	++	+++
Poor prognosis following MI	++	+++
Morbidity from MI	++	+++
CAD mortality with diabetes	++	++++
Prehospital death with acute MI	+++	++
Post-MI in-hospital mortality	++	+++
Post-PTCA complications	+	++
Post-PTCA mortality	+	++
Post-CABG complications	+	++
Post-CABG mortality	+	++

PTCA: percutaneous transluminal coronary angioplasty;
CABG: coronary artery bypass grafting; MI: myocardial infarction;
CAD: coronary artery disease

those with high Lp(a) and low HDL levels or high TC/HDL ratio. The results of the AFCAPS/TexCAPS support this recommendation. There was a 46% reduction in MACE by lowering LDL levels to <110 mg/dl in low-risk asymptomatic American women (one-fourth the risk of Indian women) with no CAD or risk factors.⁸² Statins are highly effective in reducing the TC/HDL ratio (goal <4) in women with low HDL unresponsive to lifestyle measures.⁸⁸

Hormone replacement therapy (HRT): More than 30

observational studies suggest a 35%–55% reduction in CAD incidence and mortality among women who receive HRT.⁸⁹ However, the first two randomized clinical trials of HRT failed to demonstrate any cardiovascular benefit.^{90–92} In the HERS, there was a suggestion of early harm and late benefit overall. Women who were in the highest quartile of Lp(a) levels and received HRT had an impressive 54% decrease in MACE with no suggestion of early harm.⁹³ Over 40% of Indian women have Lp(a) levels >20 mg/dl, which is associated with a high risk of CAD.^{93,94} The benefits of HRT may be greater in Indian women, who have substantially higher rates of CAD (3-fold) and lower rates of breast cancer (one-half)⁹⁵ compared with Whites.

Conclusions

CAD is the leading cause of death in women. Health care providers need to be sensitive to gender differences in presentation, prognosis and responsiveness to treatment of CAD. The prognosis of women with CAD differs according to age, mode of presentation, accuracy of diagnosis, and number of risk factors and is generally more ominous in women. The failure to treat women as vigorously as men contributes to their worse outcome although the gap is narrowing rapidly in western countries.⁹⁶ Doctors need to understand the risk as well as risk factors of CAD in women and the importance of prevention, diagnosis and timely intervention. Most of the modifiable risk factors such as obesity, smoking, hypertension, diabetes and dyslipidemia are the same in both sexes and should be identified and treated early. Reducing saturated fat in the diet and simultaneously increasing the consumption of fish, fruits, vegetables, nuts and fiber are the dietary ingredients for a healthy heart. Exercising regularly, maintaining an ideal BMI and waist size, quitting tobacco, controlling hypertension and diabetes can substantially reduce the risk of CAD and its complications. Health care systems need a paradigm shift that emphasizes a healthy lifestyle for young men and women.

Because of the high rate of CAD despite maximum modification of lifestyle, pharmacological therapy may be necessary in many Indians.⁹⁷ The underdiagnosis and undertreatment of dyslipidemia is greater in women worldwide and appears to be worse in India.⁹⁸ Use of statins for dyslipidemia should not be delayed until a cardiac catastrophe. The collective efforts of the government, professional organizations, food industry and academic community should be directed toward realizing a significant health benefit by the society. Advances in the prevention and treatment of CAD should not be denied to women.

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