



Review Article

Coronary artery disease in women



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ABSTRACT

Background: Despite the importance of CAD for women, there is persistent perception that CAD is a man's disease. Contributing to this notion is the observation of differences in incidence rates according to age; the incidence of CAD in women is lower than men, but rises steadily after fifth decade. The distribution of CAD risk factors varies between men and women across age ranges and failure to consider these differences may have contributed to the belief that women are at lower risk of CAD compared with men. In addition, women are more likely to have symptoms considered atypical compared with men. There is an urgent need to better understand the presentation of cardiac symptoms in women, in order to facilitate diagnosis and treatment, to initiate aggressive risk factor intervention and to improve the quality of life.

Methods: We studied clinical and angiographic profile of women undergoing coronary angiogram over a period of 6 years at Nanavati Hospital, Mumbai. The objectives were to examine the distribution of risk factor and coronary angiographic patterns of CAD in women.

Results: It was observed that coronary artery disease is most commonly involving females between the age 60 to 80 years. Raised LDL-C was found to be most common risk factor involved in development of coronary artery disease in females. Most common presentation of CAD in women is unstable angina or non-ST segment elevation MI. Most common coronary angiography finding was single vessel disease.

Conclusion: Though coronary artery disease is late to present in women it significantly hamper quality of life. The clinical presentation of coronary artery disease in women varies from asymptomatic to severe unstable angina to myocardial infarction. Stress testing and 2D-ECHO helps to some extent for prediction of coronary artery disease but false positive as well as false negative test results are not negligible. Coronary angiography is the conclusive test to determine spectrum and characterization of coronary artery anatomy in women. As this study is based on experience at single center, various biases may be possible. Widespread data collection involving multiple center and multiple operators will be helpful.

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1. Introduction

Coronary artery disease is the leading cause of mortality and morbidity of both men and women accounting for over one third of total deaths.¹ It has reached epidemic proportion among Indians. It accounts for 1 out of 3 women death regardless of the race or ethnicity.² In women, the annual mortality rate from CAD is high. The worldwide INTERHEART Study,³ a large cohort study of more than 52000 individual with myocardial infarction, have revealed that women have their first presentation of coronary heart disease approximately 10 years later than men, most commonly after menopause. Despite this delay in onset, mortality is increasing more rapidly amongst women than men.³ Epidemiological studies from various parts of India have reported the rising trends and a high burden in the levels of conventional risk factors such as diabetes, hypertension and metabolic syndrome.^{4,5}

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.⁷

Our study is a single center based study based on all women undergoing coronary angiography for various indications. We studied clinical and angiographic profile of women undergoing angiography at our center in 6 years. This study provides in depth understanding about distribution of coronary artery disease amongst various age group of women and its possible cause. It also compares various risk factors, clinical presentation and angiographic picture of women undergoing coronary angiography. The study helps to understand the need for coronary evaluation in women and its importance on well-being and quality of life of women.

2. Cad mortality in women

Women have poorer prognosis and more severe outcome than men after myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting. Women are more likely than men to die after a first MI, and for survivors, there is higher risk of recurrent MI, heart failure or death.⁸ In Framingham heart study the one-year mortality following an MI was 44% in women vs. 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 pre-hospital mortality.⁹ Despite their excess risk, women are only half as likely as men to receive aspirin, beta-blockers or thrombolytic therapy or to be referred for revascularization

procedure. Vaccarino et al¹⁰ found that mortality from MI in women <50 years of age was double that of men and excess mortality in women is limited to <60 years of age.

3. Risk factors in women

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 and high levels of total cholesterol, triglycerides, low-density lipoprotein and Lp (a) are correlated with CAD.¹² 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.² Prevalence of most risk factors is lower in rural than in urban India with exception of smoking/tobacco use (Tobacco Paradox).¹³

3.1. Age

Women are about 10 years older than men at first manifestation of CAD, although they have similar plaque burden.¹⁴ Women lose this 10-year advantage if they smoke, have diabetes, or had premature menopause. Prevalence of CAD is higher in men prior to fifth decade of life. During sixth decade it equalizes and subsequently it becomes greater in women. Postmenopausal increase in the risk of CAD is related to a higher incidence of hypertension, diabetes, dyslipidemia and obesity. Younger women with ACS have up to 50% higher risk for mortality than their young male counterparts.^{11,15} The higher risk of mortality in these young women may be due in part to the perception that younger women are at very low risk of CAD and therefore diagnostic and therapeutic management is minimal.

3.2. 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. Family history of CAD in a sister is associated with 12-fold higher risk vs. 6-fold for a brother and 3-fold for a parent.¹⁶ Stromelysin-1, members of the matrix metalloproteinase family of enzymes that are believed to be involved in plaque rupture and plasminogen activator inhibitor-1

(PAI-1) is associated with myocardial infarction in women.¹⁷ Difference in genetic expression leads to difference in pathophysiology of atherosclerosis including plaque composition, endothelial dysfunction and hemostasis.¹⁸ Estrogen induced coronary vasodilation adds to this. Women are twice as likely to have plaque erosion (37% in women vs. 18% in men) while men are more likely to have plaque rupture (82% in men vs. 63% in women).¹⁹

3.3. RACE – ASIAN INDIAN WOMEN

CAD rates amongst Asian Indians are higher as compared to other ethnic origins. At any given level and/or combination The CAD rates are reduced to half in the West in past 30 years, whereas it has doubled in India with no signs of downtrend yet.²⁰ Average age of first myocardial infarction has decreased by 20 years in India. CAD among Indians is at least double that of Americans and several folds higher than other Asians.²¹ Among Asian Indian, about half of all MI occurs under the age of 50 and 25% under the age of 40. This excess burden of premature CAD in Indians is due to a genetic susceptibility, mediated through elevated levels of lipoprotein a, which potentiate the adverse effects of lifestyle factors associated with urbanization, affluence and change in diet. The excess CAD mortality among Asian Indians is greater in women than in men.²² Triple vessel disease is seen among half of all Asian Indians and one third of premenopausal women.²² Indian ethnicity has now been demonstrated to be a risk factor by itself.²³

3.4. Hypertension

Hypertension confers a 4-fold risk of CAD in women vs. 3-fold in men. Hypertension tends to be more common in women than in men after 45 years of age. Systolic blood pressure continues to increase disproportionately in women until the age of 80 and it is closely correlated with obesity and is 6-fold higher in women with BMI > 30. Conversely, a weight reduction of 9 kg can lower systolic BP by 6mmHg and diastolic BP by 3mmHg in hypertensive patients.²⁴ Women have 15% higher prevalence of hypertension than in men.²⁵ Women with hypertension have more under treatment and poor control than men.

3.5. Diabetes and metabolic syndrome

Metabolic syndrome is a precursor of diabetes and a common pathogenic mechanism for the development of CAD. This syndrome is particularly common among Indians. This is different from the cardiac syndrome X²⁶ (angina with abnormal treadmill test and normal coronary angiogram), which is more prevalent in women. Both diabetes and metabolic syndrome are equally prevalent in women. CAD is twice as common among women with diabetes as those without. In the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), diabetes is regarded as a CAD risk equivalent.²⁷ 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.²⁸ 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.²⁹ The INTERHEART study confirmed the strong association between diabetes and myocardial infarction among women compared with men.³ Premenopausal women with diabetes faces a similar risk of developing CAD as nondiabetic men of the same age.³⁰ Following an MI, diabetic women have double the rate of recurrence and shorter survival than men.

3.6. Diabetic dyslipidemia

Approximately 80% of deaths in diabetic patients are attributable to CAD, which in turn is highly correlated with dyslipidemia.³¹ Diabetic dyslipidemia consists of elevated TG, low HDL and 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.²⁷ 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.

3.7. HYPERLIPIDEMIA

Many studies observed a rise in triglyceride and LDL cholesterol with menopause.³² Indian women tends to have low level of HDL compared to others.

3.7.1. Total cholesterol (TC)

Its level in women is 10 mg/dl lower compared to men before the age of 45. But beyond 65 years of the age reverse is true, means its 10 mg/dl higher in women. 20% difference in TC level is associated with a 50–60% increase in CAD risk over lifetime.³³ Optimum level of TC recommended is <160 mg/dl.

3.7.2. LDL

Its strong predictor of CAD mortality in women as well as in men. LDL level increases steadily by an average of 2 mg/dl/year between the age of 40–60 years.³⁴ Optimum level of LDL is <100 mg/dl.²⁷

3.7.3. HDL

Low HDL is an important risk factor even if TC and TG levels are normal. It is a strong predictor of CAD in women than in men especially after the age of 65. HDL level are about 10 mg/dl higher in premenopausal women than in men. Indian women found to have lowest level of HDL compared to women of other ethnic origin. HDL level among Indian women is about 10 mg/dl lower than in whites and 20 mg/dl lower than in Blacks, the Chinese and Japanese. Lower level of HDL in Indian women parallels their high rates of CAD.³⁵ The NCEP ATP III has classified HDL < 40 mg/dl as low and >60 mg/dl as high HDL.²⁷ Many experts consider HDL < 50 mg/dl to be low in women. In the Coronary Artery Disease in Indians (CADI) study,³⁶ 70% of Indian women had HDL level < 50 mg/dl. If the level is < 35 mg/dl, it confers a 8-fold higher CAD risk than an HDL > 75 mg/dl in women.³⁷

3.7.4. Total cholesterol/HDL ratio

This ratio is now widely recognised 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. Indian women worldwide have a high TC/HDL ratio by virtue of low HDL, even when TC level are not elevated.³⁸ Optimum TC/HDL ratio is 3 and average ratio is 4. Ratio more than 5 appears to be a strong predictor of CAD and is observed in 25% of industrial and 32% of urban female populations in India.⁶

3.7.5. Triglycerides

A high TG level is a strong 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 vs. 30% in men.³⁹ Low TG (<97 mg/dl) and high HDL (>57 mg/dl) is associated with very low risk of CAD,⁴⁰ but is uncommon among Indians. Optimum TG level is <150 mg/dl.

The combination of high TG, low HDL and high small dense LDL is called 'lipid triad'. All these abnormalities are common among

Indian men and women, rendering them highly susceptible to CAD.⁴¹

3.7.6. LIPOPROTEIN (a)

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. Lp(a) is a stronger determinant of CAD in premenopausal than in postmenopausal women. High level 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. Combination of all four of the above increases the risk of CAD by a factor of 122.⁴² Lp(a) was a powerful predictor of mortality in the 4S study.⁴³ Lp(a) appears to be a stronger risk factor than diabetes in young women. Although Lp(a) levels are largely genetically determined, there is a 10% increase in Lp(a) level in postmenopausal women. Hormone replacement therapy reduces Lp(a) by an average of 20% in women with high Lp(a) levels.⁴⁴

3.8. Obesity and physical activity

Obesity is associated with increased risk of hypertension, diabetes, dyslipidemia and CAD. Body Mass Index (BMI), is now accepted as the single best measure of obesity.⁴⁵ In the 16 year data from the Nurses' Health Study (NHS), CAD mortality was 4-fold lower in lean (BMI < 21) than in obese women.⁴⁶ For Asians, the optimum BMI is < 23, whereas > 23 is considered overweight and > 25 obese. The prevalence of obesity is increasing amongst Indian women. Most female did not engage in leisure-time physical activity and 18.5% were smokers.⁴⁷

3.9. Tobacco abuse

Due to its anti-estrogenic effects, smoking quadruples the risk of MI in young premenopausal women. It is a strong risk factor in women than in men. 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. The overall rate of smoking is low among Indian women, particularly in urban areas.

3.10. Passive smoking

Only 8% of the women in Asian countries smoke compared to 60% men who smoke.⁴⁸ Therefore vast numbers of women and children are exposed to environmental tobacco smoke, 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.

3.11. Socioeconomic status and psychosocial factors

CAD has now become a disease of the poor in rich countries and of the rich in poor counties. Women with a 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. Indians with low literacy have a higher prevalence of CAD and risk factors such as smoking and hypertension. In addition, healthy life-style choices namely regular exercise, fruit and vegetable intake and modest alcohol consumption provided stronger protection among women than men. The impact of psychosocial and behavioral factors on CAD in Indian women requires further investigation.²⁰

4. Patterns of presentation

First presentation of CAD in women may be chest pain, myocardial infarction, heart failure or sudden cardiac death.

4.1. Angina/chest pain

Women are more likely to initially present with chest pain than a more clearly defined event such as myocardial infarction. In a 26 year follow up from the Framingham study, angina was uncomplicated in 80 percent of women, whereas it evolved out of infarction in 66% of men.⁴⁹ Women are less likely than men to have typical angina (28 versus 55% in review of over 3100 patients undergoing exercise stress testing)⁵⁰ Another factor important in the interpretation of chest pain in women is the greater likelihood of angina being induced by rest, sleep and mental stress in addition to or instead of physical exertion.⁵¹

Effort angina pectoris, due to reversible myocardial ischemia, caused by obstructive CAD that limits blood flow during periods of increased myocardial oxygen demand. This mode of presentation did not appear to afflict women until they became elderly with the exception of diabetic women.⁵²

Due to above observations, women who present to emergency department with new onset chest pain are approached and diagnosed less aggressively than men.⁵³

4.2. Syndrome X and microvascular dysfunction

Endothelial dysfunction, and higher risk of atherosclerosis is prevalent in women with hypertension, diabetes and dyslipidemia.⁵⁴ In WISE study, only 39% of the women had CAD, defined as over 50% stenosis. WISE study⁵⁵ concluded that the typical angina classification missed 65% of women who actually had CAD. Symptoms experienced by women without CAD may be related to micro-vascular ischemia or vasospasm of coronaries.

4.3. Acute coronary syndromes

Milner and colleagues studied 127 men and 90 women.⁵⁶ They concluded, amongst patient presenting to emergency department with symptoms of coronary disease other than chest pain, there were several sex-related differences in symptoms. Dyspnea, nausea/vomiting, indigestion, fatigue, sweating and arm or shoulder pain as presenting symptoms in the absence of chest pain was more frequent among women than men. Many cases of myocardial infarction in women go unrecognized, particularly at younger ages. In a study from Iceland, the frequency of unrecognized MI was found to be 1.3 per 1000 at age 35 to 60 per 1000 at age 75.⁵⁷ In HERS trial, 9.3% women found to have ECG evidence of an MI that was unrecognized clinically in 46%.⁵⁸

4.4. Other presentations

Other presentation of CAD in women is Heart Failure and Sudden Cardiac Death.

5. Coronary angiography

The prevalence of significant coronary disease found at the time of angiography is lower in women than men presenting with chest pain.⁵⁹ Normal coronary arteries is much more common in women compared to men (41% vs. 8%)⁶⁰ possible mechanisms for the absence of significant coronary disease in these patients include rapid clot lysis, vasospasm and coronary micro vascular disease.

One of the largest reports of angiographic findings in young patients with CAD comes from a sub study of the CASS trial. This trial concluded following

- Young women had a higher frequency of angiographically normal coronary arteries than young men.
- Single vessel coronary disease was more common (38 vs. 24%) and triple vessel disease (14 vs. 39%) was less common in younger patients.

5.1. Aims and objectives

Our study aimed at studying clinical profile of women undergoing angiography at our center. We studied various risk factors and their association with occurrence of coronary artery disease. Our study tried to determine age distribution and possible reason for the same. We also compared amongst various angiographic pattern amongst women undergoing coronary angiography for various reasons.

5.2. Study profile

In this retrospective analysis of women, who underwent coronary angiography during past 6 years at our center, we studied various presentation for which coronary angiography was conducted. Females who had already undergone coronary revascularization (PCI or CABG) in past are excluded from the study. The data was analyzed for various age group and the coronary angiography findings. The risk factor profile was studied in terms of presence of hypertension, diabetes mellitus, hyperlipidemia, smoking and tobacco abuse.

Total 3250 females underwent coronary angiography in past 6 years due to various reasons. In our analysis we found the CAD was most prevalent between the age group 60–80 years. Out of 3250 65% were post-menopausal and 24% were post hysterectomy. Total 54% females were vegetarian in our study population, whereas 46% was having mixed diet. Out of females consuming mixed diet, 26% eats red meat and rest 74% did not. The risk factor profile revealed association of raised LDL (76%), Diabetes mellitus (63%), reduced HDL (55%) and obesity (54%). Active smoking was present only in 7% patients. The family history of Coronary artery disease (in 1st degree relatives) was found to be present in 49% of women. Retrospective analysis of the presenting complains found that most common indication to perform angiography was unstable angina/NSTEMI (51%) followed by Stable Angina (25%) and Myocardial infarction/STEMI (13%). True positive stress test was found in 1352 patients, whereas false positive in 482 patients. ECHO findings varied from Good LV function (1432 patients) to poor LV function (682 patients). Many were not evaluated either by Stress test or Echocardiography.

Analysis of the diagram of coronary angiographic findings showed that women most commonly suffered from single vessel disease (51%) followed by triple vessel disease (27%), double vessel disease (07%). Normal coronaries found to be in 15% of women undergoing coronary angiography. Out of total 4591 lesions, 51% were Type A, 27% were Type B and 22% were Type C. Calcification was found to be associated with 365 lesions. Left main disease was found in 156 females whereas ostial lesion in 144 and bifurcation disease was in 632 women. 256 had diffuse lesion involving either one or more coronary arteries.

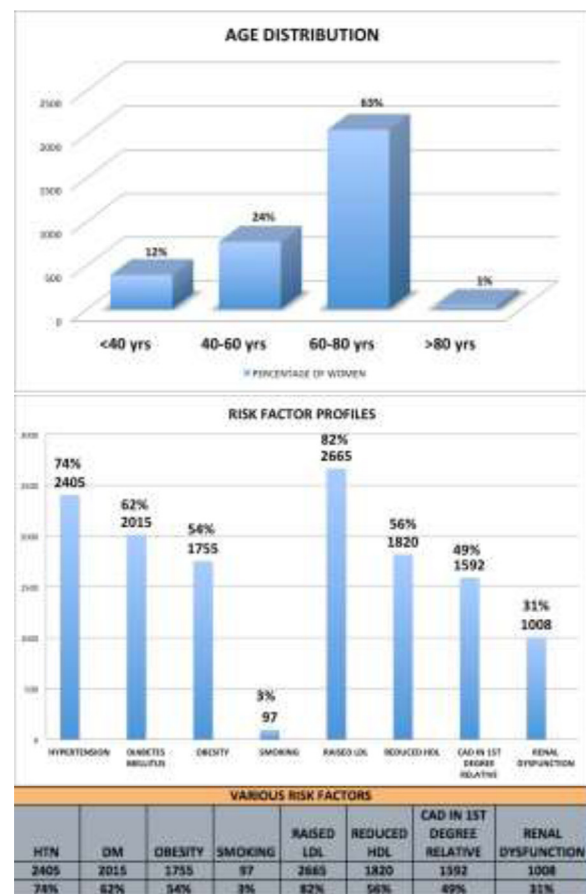
6. Conclusion

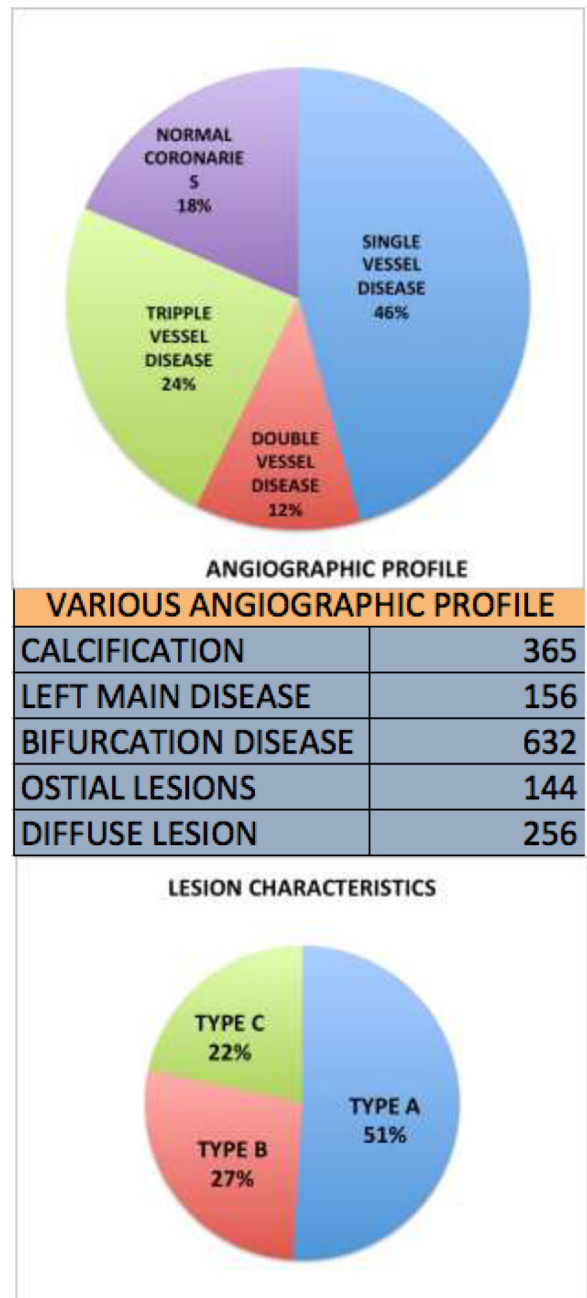
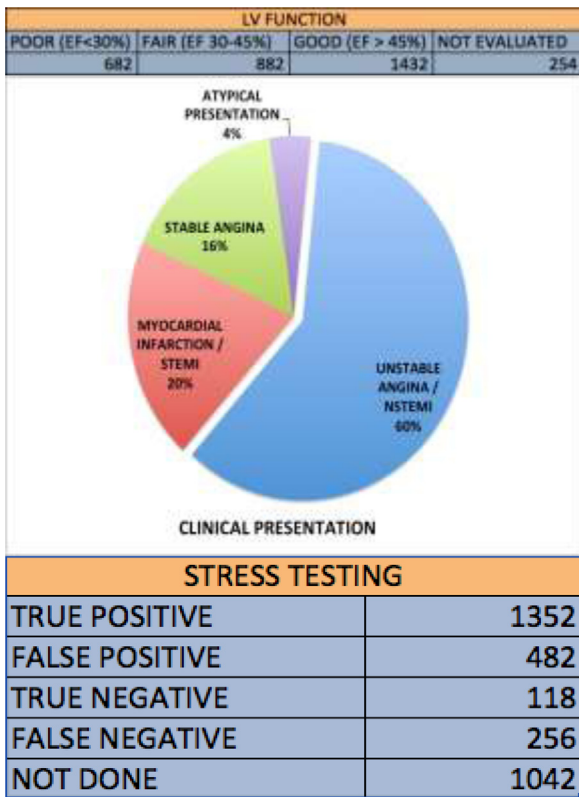
CAD in women continues to be a major public health problem that represents a leading cause of death and disability. Women

have varied presentation of coronary artery disease. They can present as asymptomatic with borderline positive non-invasive testing. They can also present as frank myocardial infarction. Age distribution of coronary artery disease amongst women showed that elderly women are more affected, this can be secondary to post menopausal status. This fact denotes the role of estrogen and other female reproductive hormones with occurrence of coronary artery disease. To day estrogen as a protective factor for coronary artery disease, wide spread study with multiple parameters is recommended. Various risk factors including smoking and family history of premature CAD is noted in our study. Women have varied presentation of coronary artery disease from single vessel disease to multi vessel disease. Characteristics of coronary lesion also vary widely amongst women.

Conflict of interest

None.





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