ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 10, Issue, 03(D), pp. 31440-31445, March, 2019

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

DIFFERENCES BETWEEN MALE AND FEMALE PATIENTS WITH ACUTE CORONARY SYNDROME REGARDING CLINICAL PROFILES AND OUTCOMES. A REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2019.1003.3261

ARTICLE INFO

Article History:
Received 15th December, 2018
Received in revised form 7th January, 2019
Accepted 13th February, 2019
Published online 28th March, 2019

Key Words:

ACS- Acute coronary syndrome
CAD- Coronary Artery Disease.
UA- Unstable angina.
NSTEMI- Non ST segment elevation Myocardial Infarction.
STEMI- ST segment elevation Myocardial Infarction.
CABG- Coronary Artery Bypass Graft.

ABSTRACT

Background: Coronary artery disease (CAD) has emerged as a major health burden in developing countries. Acute coronary syndrome is composed of patients with acute myocardial infarction (MI) with ST segment elevation on their presenting electrocardiogram (STEMI) and those with unstable angina (UA) and non-ST-segment elevation MI (NSTEMI). Many recent reports concluded that women with CAD have a worse prognosis than men and also with regards to invasive interventions when compared to men.At any given age the prevalence of CAD is greater in men when compared to women. Nonetheless, many recent reports concluded that women with CAD have a worse prognosis than men with this disease. We review various observational articles, clinical studies, outcomes of ACS in various studies from electronic databases (PUBMED and Cochrane Central Register of Controlled Trials) for potentially relevant articles comparing various studies. The aim of this review is to study whether there is any significant difference between the clinical profile and outcomes in male and female patients with ACS.

INTRODUCTION

Cardiovascular diseases have emerged as a major health burden in developing countries. Significant differences in the prevalence of coronary artery disease (CAD) exist with respect to gender, age, and ethnicity. It is predicted that the prevalence of acute coronary syndrome in India will be more than 50%of the worldwide figure. In 2003, the prevalence of CAD in India was estimated to be 3–4% in rural areas and 8–10% in urban areas (six-fold higher compared with 40 years ago)[1]. In all the post-menopausal women and age matched men, the prevalence of CAD is equal. At any given age the prevalence of CAD is greater in men when compared to women. Nonetheless, many recent reports concluded that women with CAD have a worse prognosis than men with this disease[2].Acute coronary syndrome is composed of patients with acute myocardial infarction (MI) with ST segment elevation on their presenting electrocardiogram (STEMI) and those with unstable angina (UA) and non-ST-segment elevation MI (NSTEMI). STEMI is due to the formation of occlusive thrombosis at the site of rupture of an atheromatous plaque in a coronary artery and is diagnosed by presence of pathological Q waves, a raisedcoved ST segment with symmetrical T wave inversion. UA is defined as angina pectoris or equivalent ischemic discomfort with at least one of the three features- 1) It occurs at rest (or with minimal exertion); usually lasting > 10 min.2) It is severe and of new onset (i.e., within prior 4 to 6 weeks), and/or3) occurrence with a crescendo pattern (i.e., distinctly more severe, prolonged, or more frequent than previously).

The diagnosis of NSTEMI is established if a patient with clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac enzymes. UA/NSTEMI is usually associated with severe coronary obstruction but not total occlusion of the culprit artery. Those patients who have evidence of elevated enzymesand without ST segment elevation in ECG are diagnosed as NSTEMI[4]. In this, we try to determine the clinical profile and severityof ACS in women compared with men by looking at various articles and studies from various journals and websites.

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METHODS

In this article, we review various observational articles, clinical studies, outcomes of ACS in various studies from electronic databases (PUBMED and Cochrane Central Register of Controlled Trials) for potentially relevant articles comparing various studies. Keywords used for search included: ACS- Acute coronary syndrome, CAD- Coronary Artery Disease.

UA- Unstable angina. NSTEMI- Non ST segment elevation Myocardial Infarction. STEMI- ST segment elevation Myocardial Infarction. CABG- Coronary Artery Bypass Graft.

EPIDEMIOLOGY

VeenaNanjappa *et al*[5] in Karnataka in 2015 studied 133 successive cases of women presenting with ACS, who met the inclusion criteria, between 2012 and 2014. Cases were grouped into ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). They have concluded Diabetes was present in 58.3% in NSTEMI, 65.1% in STEMI, and 57.1% in UA group. Hypertension was found in 75% of NSTEMI, 60.2% of STEMI, and 71.4% of UA group. Severe MR was found in 11.1% of NSTEMI and 3.6% of STEMI patients. 8.3% of NSTEMI and 15.7% of STEMI patients presented in Killips class IV. Single vessel disease was most commonly found across the spectrum of ACS. 68.7% patients in STEMI group underwent primary angioplasty.5.6% of NSTEMI and 7.2% in STEMI group had contrast-induced nephropathy (CIN). All deaths were noted in STEMI group with eight in-hospital deaths and three during 30-day follow up[5].

Coronary Artery DiseaseWomen Versus MenIncidence Of Coronary Artery Disease CAD in the entire lifetime is more common as a cause of mortality in women than men[6]. Analysis have indicated worse prognosis and increased death in women. The excess CAD death is attributed to the greater age of women, which is an extremely powerful risk factor in its own right. The delay in onset in women compared to men is presumably due to pre-menopausal exposure to endogenous ovarian estrogen[7].In females, CAD is increased around the time of menopause when the estrogen in plasma begins to decline. It is observed in studies that atheromatous fatty streak and atheromatous plaque exist both in men and in women. The extent of fatty streak in both men and women is a function of plasma level of LDL cholesterol and in women, VLDL cholesterol, which is closely related to the triglyceride level. The lesions in femaleare more lipid filled, rich in macrophage and less densely fibrous[7]. Thus the lesion will be at times more unstable.

Black women are more susceptible than whites for acute MI. This prediction is borne out by national mortality data where black women have consistently had a 50% - 75% greater risk for death from diseases of heart[8]. The reasons for this greater risk are unclear but could relate to the particular mix of CAD risk factors.

The social difference is greater in women compared to men; women with poor socioeconomic status have nearly four times the standardized mortality ratio of richer women. The tendency to overlook CAD in women is because of its lesser frequency in young and middle age and compounded by less classical presentations. More frequently CAD presents as angina in women and MI in men. In the Framingham study, the annual incidence of angina pectoris in women exceeds that of MI by ratio more than 2:1 in age 45 to 54 and 55 to 64, whereas in male MI incidence exceeds angina in all ages[9,10]. This gives the clinical impression that angina pectoris is an earlier and most common presentation in women.

Recognition of chest pain of cardio vascular etiology in women is difficult to diagnose because:a) Atypical, non-cardiac chest pains are more common in women compared to men b) True angina may not be typical.

Because of atypical symptoms misdiagnosis is common. The reason for lack of classic angina symptom in spite of having validated myocardial ischemia is unknown. The greater incidence of silent MI in womenmay be related to atypicality of chest pain presentation[6].

Exercise tolerance test is to clarify atypical chest pain is not as useful in females as in males because of the susceptibility for false positive results[6]. Decision to perform exercise test is decided by the number of risk factors in the patient. The more the risk factors, the more likely the test will be a true positive.

There is a possibility for a female patient having chest pain and positive exercise test and negative angiogram with normal lumen to have vaso-spastic disorder.

Risk Factors

Risk factor reduction is the primary clinical approach to prevent coronary artery disease (CAD) morbidity and mortality. The concept of risk factor identification and modification is based on the fact that exposure to certain host and environmental factors increases the statistical risk for developing a disease and that alteration of these conditions reduces the risk. Thus identifying risk factors may possibly retard the formation and growth of an atherosclerotic plaque.

The Framingham studywas first of its kind to describe the primary and secondary risk factors like hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, obesity, race, family history of coronary artery disease, physical inactivity and personality type[9]. Anderson et. al. concluded that the relative effects of serum cholesterol, hypertension and smoking were equal in both sexes[11].

Women have the same risk factors like men. Although age, menopause, diabetes mellitus, low HDL cholesterol, and the use of oral contraceptives, may play an additional role in the development of coronary artery disease.

The Risk Factors for CAD are Divided into

Modifiable Risk Factors

Major

1. Cigarette smoking.
2. Hypertension.
3. Diabetes mellitus.
4. Hyperlipidaemia.
5. Obesity

Minor Risk Factors

A) Oral contraceptives. B) Physical activity. C) Personality.D) Socioeconomic status (SES) and psychosocial factors. E) Others–Alcoholism, Hyperuricemia, Hyperhomocystinemia, Excessive Coffee consumption, Deficiency of trace elements, Low circulating levels of antioxidants etc.

Non Modifiable Risk Factors

1. Age.
2. Race.
3. Family history.
4. Gender

Major Modifiable Risk Factors

Cigarette Smoking: Smoking is a well-documented risk factor for coronary artery diseases. Women, who smoke, are 3.6 times more likely to have a myocardial infarction than non-smokers. The incidence of sudden death is higher in smokers than in non-smokers. Cessation of smoking in high-risk individuals is followed by reduction in risk of coronary artery disease[11]. It may take 2-3 years for the risk to equal non-smokers, after cessation of smoking[13].

Cardiovascular mortality increased by 18% in men and 31% in women for identical smoking consumption[14]. Smoking has a synergistic effect on coronary artery disease mortality in individuals with other risk factors[13]. Passive smoking may also increase risk for CAD. Subjects who live with current or former smokers were prone to CAD by 9.6% in men and 6.1% in women**.**

Hypertension

Numbers of studies have conclusively proved the role of hypertension in the development of coronary artery diseases. The risk of development of CAD is continuous and graded. According to data from Framingham study11, hypertension is associated with two fold increases in risk for CAD. The same study also interpreted that the proportion of MI is not only twice that of normotensives but the incidence of infarction that go unrecognized significantly increases with the severity of hypertension and is twice as that of normotensives[15].

Diabetes Mellitus

Women are particularly vulnerable to the cardiovascular sequelae of diabetes[16].Among patients evaluated for symptomatic coronary artery disease women are more likely than men to have diabetes mellitus. Atherosclerosis occurs earlier in diabetics[17]. Thus, diabetic women tend to have an excess of the major risk factors, predisposing them to CAD. These are often present even before diabetes mellitus manifests. All these atherogenic traits are further aggravated when diabetes is overtly manifested[18].

Diabetes increases the risk by 3 fold in women. Women with diabetes do not share the relative gender mediated pre-menopausal protection against CAD[17].

In Framingham study, diabetic women had three-fold higher risk for recurrent MI and two-fold higher risk for fatal re-infarction than non-diabetic women[11]. TIMI data reveals, that diabetic women treated with thrombolysis had twice in hospital mortality compared to diabetic men and 4 times the mortality of non-diabetic men. Diabetes increases the risk of heart failure by 8 fold in women as compared to 4 fold in men. Diabetes eliminates the protective effects of estrogens and removes the normal sex difference in the prevalence of CAD[18].

Blood Lipids

Total cholesterol (TC), High-density lipoprotein (HDL) and triglyceride levels predict CAD independently in men and women. However, the inverse relationship between HDL and CAD risk is stronger in women. Women tend to have lower serum cholesterol levels until 50 years and then they start to exceed men's level.

According to Framingham study[11], the ratio of TC (Total cholesterol) to HDL cholesterol rises steadily with age from 3.4 at age 25-34 years to 4.7 at the age of 75-89 years. The net result is an increase in TC to HDL ratio as the age advances. However, virtually at all ages HDL values in women are 10 mg/dl higher than those in men. These changes may explain the rarity of CAD in young women and the gradualequalization of risk with advancing age. All atherogenic lipids rise with age till about 60 years and then decline[11,16].

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 square metres (kg/m^2) is now accepted as the single best measure of obesity[19].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[20]. For Asians, the optimum BMI is <23, whereas >23 is considered overweight and >25 obese[20]. Thus the BMI cut-off points for overweight are two units and obesity 5 units lower in Asians than in Whites.

Minor Risk Factors

Oral Contraceptives (ocp's)

Oral contraceptive predisposes women to CAD at a much younger age. Patients on OCP's have been found to accelerate blood clotting and decreased blood concentration of some clotting factors[13].

Mann et. al was the first one to demonstrate the increased risk of MI with OCP's. The relative risk of MI was 4-5 times more when compared to non-user. Smoking along with OCP has increased the risk of CAD especially after 35 years. It thus has a synergistic effect leading to early menopause. Use of OCP's and smoking in pre-menopausal women, increase the incidence of MI 7-39 times more than non-smoking and non-pill users[21].

Physical Activity

The Framingham study shows sedentary people had about 3 times more risk of developing CAD than a physically active person. Postulated mechanisms for favorable effects of physical activity include: 1) Exercise induced increase in HDL and Lipoprotein lipase levels. 2) Increase in myocardial oxygen demand for any sub maximal task. 3) Decrease in platelet adhesiveness and increased fibrinolytic activity. 4) Improves myocardial perfusion. Thus, exercise can be recommended as a

strong adjuvant to dietary modification in prevention and treatment of obesity[13,33].

Personality

Type A personality is associated with higher risk of CAD in women[34]. Depression is associated an increased risk of fatal CAD in women.

Socioeconomic Status (Ses) and Psychosocial Factors

CAD has now become a disease affecting all socioeconomic status people in developing countries. Women with less than a high school education have a 30%-50% higher CAD mortality than those with higher education. Depression, 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 three to four fold higher odds ratio for a high-risk lipid profile, after controlling for SES, age and sex[22]. The impact of psychosocial and behavioral factors on CAD in Indian women requires further investigation.

Others

Alcohol

In low to moderate quantity, it is protective due to increase in HDL and inhibition of platelet aggregation. In large doses, it is harmful[23].

Diet

Certain dietary practices like high consumption of saturated fats, sucrose, animal fats and less of vegetable are associated with increased risk of MI. A high fiber diet is recommended.

Non- Modifiable Risk factors

Age: Compared with the age group 34-44, CAD mortality among women increases 40- fold by the age of 80, when its incidence becomes 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.

Asian Indian Ethnicity: The risk of CAD among Indians is double that of Americans and several-fold higher than other Asians. Indian ethnicity has now been demonstrated to be a risk factor by itself[24].

Family History: Studies suggest that the familial aggregation of coronary artery disease may be influenced by genetic characteristics of risk factors and by common environmental factors (such as diet, smoking, exercise habits) encountered by family members[25]. The genetics of CAD appears to be a complex interaction of – genetics, molecular and cell biology and environmental issues. At present, it is estimated that about 40% of the risk of developing CAD is controlled by genetic factors and 60% by environmental factors.Among women, a history of MI or sudden death before the age of 55 years 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 six fold for a brother and three fold for a parent[26].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.

Menopause: CAD is now a major cause of morbidity for both men and women. In women, death occurs at a later age than men, with CAD developing a decade later. This discrepancy in CAD between the sexes has been attributed to hormones and menopause.

Cardiovascular Consequences of Menopause[27,28]

- Hemodynamic changes- A gradual increase in peripheral vascular resistance is seen after menopause due to lack of estrogen effect on the receptors in the muscular layers of arterial wall. There is also a decrease in contractility, stroke volume and LV function.
- There is an increase in Endothelin-1 after menopause, which is a powerful vasoconstrictor.
- Estrogen has calcium antagonistic properties. After menopause, there is an increased calcium influx, leading to increased peripheral vascular resistance.
- Hemostatic factors like Fibrinogen, PAI-1 and factor VII are increased, thereby predisposing atherogenesis.
- Changes in lipid and carbohydrate metabolism – there is an increase in TC, LDL and a decreasein HDL levels.
  There is an increase in insulin resistance, thereby leading to smooth muscle hyperplasia. This is due to hyperinsulinemia.

Framingham study demonstrated menopause doubled the risk of CAD. There was prompt loss of resistance to CAD in post-menopausal women compared to those of the same age who were pre-menopausal. The type of menopause whether natural or surgical conferred the same risk[11].

Hormone replacement therapy (HRT) has gained importance as a primary prevention of CAD. (Various studies show that there is 15-25% reduction in mortality with HRT and morbidity from cardiovascular disease is reduced by 50-85%[27,28,29,30].

Siwach SB *et al* in a study of ACS in 338 young patients, have reported that Male: Female ratio is 20:1 and among them 68% were diagnosed as anterior wall MI and Smoking was found to be the major risk factor (87%) in men and dyslipidemia was major risk factor in women. Overall mortality was very less when compared with older age group patients[35].

Xavier D *et al* in a study done in Kerala stated that prevalence of hypertension and Diabetes Mellitus was higher among NSTEMI/UA cases when compared to STEMI cases as observed by the CREATE registry investigators. Higher proportions of NSTEMI/UA cases in our study, when compared to those from CREATE registry,12 received beta blockers (77.6% vs. 61.9%), lipid lowering drugs (71.3% vs.

53.9%) and ACE inhibitors or angiotensin II blocking agents (67.2% vs. 51.2%) whereas the proportion of cases that received anticoagulants was less (71.1% vs. 85.5%) and the use of antiplatelet agents was similar in both the groups[32].

Table 1 Comparison of risk factors from various studies

RISK FACTORS	Yavagal *et al*[39]	Chatterjee *et al*[40]	Dave *et al*[41]	Stone *et al*[42]	Babu *et al*[43]
Menopause	30	97.7	84	-	-
Diabetes Mellitus	35	56	44	10	40.8
Hypertension	30	25	53	54	48
Family History	15	7	51	30	37.2
Smoking	10	1.3	-	-	18
Alcohol	18	14	-	-	-
Dyslipidemia	20	25	81	51	56.6

M Nazarova *et al* and Greco *et al* noted that Antiphospholipid antibodies present predominantly in males is also a major risk factor for myocardial infarction which indicate the possible involvement of autoimmune factor in pathogenesis of Myocardial infarction[36,37].

Clinical Features

After 75 years, CAD occurred equally in men and women. Epicardial coronary artery disease occurred in more than 90% of men presenting with typical angina, compared to only 60-70% in women[38]

Complications

Table 2 Comparison of complications in male and female patients from Hochman *et al* study

Complications	Hochman *et al*[44] (MALE)	Hochman *et al*[44] (FEMALE)
Nil	75	73
MR	2.4	1.4
ARI	5.6	10.2
CHB	0	0
ICH	0	0
Ischemic DCMP	0	0
AF	4.2	0
VF	1.3	2.9
VT	4.3	4.2

Mortality

Table 3 Comparison of mortality in male and female patients from 3 studies

GENDER	Hochman *et al*[44] %	Stone *et al*[42] %	Culic *et al*[45] %
Female	17.5	9.3	21.4
Male	12.3	2.3	2.8
Ratio	1.42:1	3.32:1	1.76:1

CONCLUSION

Atypical presentation of ACS was more common in females.ACS is more common in Post-Menopausal women.Women with acute coronary syndrome had higher complications and higher inhospital mortality compared to men.There is a need to create awareness on risk factor control and lower threshold to be kept for early intervention of CAD among women.A multicenter study with large sample size may be needed to design a specific protocol for the management of ACS in women.

References

1. Nag T, Ghosh A. Cardiovascular disease risk factors in Asian Indian population: A systematic review. J Cardiovasc Dis Res. 2013 Dec;4(4):222–8.
2. Laslett LJ, Alagona P, Clark BA, Drozda JP, Saldivar F, Wilson SR, *et al*. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am CollCardiol. 2012 Dec 25;60(25 Suppl):S1-49.
3. Cannon CP, Braunwald E: Unstable angina and non-ST-elevation myocardial infarction, in Harrison's principles of internal medicine,16th ed, Kasper *et al* (eds). McGraw-Hil,NewYork;2005:1444-47.
4. Gunda H R Rao, White JG. Coronary Artery Disease – An Overview of Risk Factors. Indian Heart J 1993; 45(3):143-153.
5. VeenaNanjappa a, GopiAniyathodiyil b, R. Keshava b Clinical profile and 30-day outcome of women with ACS as a first manifestation: A single-center observational study. 8 (2 0 1 6) 1 6 4 – 1 6 8.
6. Berenson GS, Wendy A Waltingey, Richard E, William. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years studied at necropsy. Am J Cardiol.1992; 70:851-58.
7. Janowitz WR, Agatsion AS, Kaplan G, Viamonte M. Differences in prevalence and extent of Coronary calcium detected by ultra-fast CT in asymptomatic men women. Am J Cardiol. 1993:72:247-254.
8. Dustan HP. Coronary artery disease in Women. Can J Cardiol 1990; 6 Suppl.B:19B-21B.
9. Lerner DJ Kannel WB. Patterns of coronary artery disease, morbidity and mortality in the sexes: 26 years of Framingham follow up. Am Heart J 1996; 111:383-90.
10. Jenkins JS, Flaker GC, Nolte B, Price LA, Morris D, Kurz J. *Et al*. Causes of higher in hospital mortality in women than men after acute myocardial infarction. Am J Cardiol 1994; 73:319-22.
11. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. Circulation. 1991; 83:356–362.
12. Antaman EM, Braunwald E: Acute myocardial infarction. In: Braunwald's heart disease. A text book of cardiovascular medicine, 7th ed, DP Zipes *et al* (eds). Philadelphia, WB Saunders; 2005.1167-1226.
13. Kannel WB. Smoking and hypertension as predictors of cardiovascular risk in population studies. J Hypertension Suppl-8: S3, 1990.
14. Sigurdsson G. Interaction between a polymorphism of the apo A-I promoter region and smoking determines plasma levels of HDL and apo A-I. Arterio-Scler. Thromb 1992; 12:1017.
15. Rosenman RH, Sholtz RI, Brand RJ. A study of comparative blood pressure measures in predicting risk of coronary artery disease. Circulation 1976; 54:51-58.
16. Barrett-Conner E L, Cohn BA, Wingard DL, Eldeslein SL. Why diabetes mellitus a stronger risk factor for fatal

ischemic heart disease in women than in men? The Rancho -Bernardo Study. JAMA 1991; 265:62.
17. Sainani GS, Sainani R. Coronary Artery disease in women. JIMSA 2000; 13(2):103-106.
18. Colwell JA, Winocour PD, Virella Ml, Halushka PV. New concepts about the pathogenesis of atherosclerosis in diabetes mellitus. Am J Med 1983; 75:67-80.
19. Redefining obesity and its treatment - the Asia-Pacific perspective 2000: International Diabetes Institute in Australia and WHO.www.diabetes.com.au/research/report_obesity.htm Accessed 6 June. 2001
20. Wilson PWE, Garrison RJ, Castelli WP. PostmenopaUAlestrogen use, cigarette smoking and cardiovascular morbidity in women over 50. The Framingham Study. N Engl J Med 1985; 313(17):1038-43.
21. Hayens SG, Finley M. Women, work and Coronary Artery disease. Prospective findings from the Framingham study. Am J Public Health.1980; 70:133-41.
22. Kornowski R. Lansky AJ, Mintz GS. Kent KM. Pichard AD. Satler LF. *et al*. Comparison of men versus women in cross-sectional area luminal narrowing, quantity of plaque, presence of calcium in plaque and lumen location in coronary arteries by intravascular ultrasound in patients with stable angina pectoris. Am J Cardiol 1997; 79*:* 1601-1605.
23. Anand SS. Yusuf S, Vuksan V, Devanesen S. Teo KK. Montague PA. *et al*. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: The Study of Health assessment and Risk in Ethnic groups (SHARE). Lancet 2000: 356:279-284.
24. Epstein IH. Hereditary aspects of coronary artery disease. Am Heart J 1964; 67:445.
25. Hamby RI, Brook NYS. Hereditary aspects of coronary artery disease. Am Heart J 1981; 101:639.
26. Mathews KA, Meilan E, Kuller LH, Kelsey SF, Caggiulo AW, Wing RR. Menopause and risk factors for coronary artery disease. N Engl J Med 1989; 321:641- 46.
27. Nayar A, Mahajan AU, Bansal NO, Vaidya SV, Pathak L. Hormone replacement therapy in postmenopausal women for cardio protection. J AssocPhys India 1998; 46:294-98.
28. Stampfer MJ, Wilett WC, Colditz GA, Rosner B, Spiezer FE, Hennekens CH. A prospective study of postmenopaUAl estrogen therapy and coronary heart disease. N Engl J Med 1985; 313(17):1044-49.
29. Stampfer MJ, Colditz GA, Wilett WC, Manson JE, Rosner B, Spiezer FE, Hennekens CH. Postmenopausal estrogen therapy and cardiovascular disease. Ten- year follow –up from nurse's health study. J AssocPhys India 1991; 325:756-62.
30. Sullivan JM,VanderZwaag R, Lemp GF.*et al*. Postmenopausal estrogen use and coronary atherosclerosis. Ann Intern Med 1988; 108:358-63.
31. Siwach SB, Singh H, Sharma D, Katyal VK. Profile of young acute myocardial infarction in Harayana. J Assoc Physicians India 1998; 46:424-6
32. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, *et al*. Treatment and outcomes of ACS in India (CREATE): a prospective analysis of registry data. Lancet 2008; 371(9622): 1435-42.
33. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An Update on the Framingham study N Engl J Med 1984; 311:1144-1147.
34. Whitty CJ. Brunner EJ, Shipley MJ. Hemingway H *et al*. Differences in biological risk factors for cardiovascular disease between three ethnic groups in the Whitehall II study. Atherosclerosis 1999; 142: 279-286.
35. Siwach SB, Singh H, Sharma D, Katyal VK. Profile of young acute myocardial infarction in Harayana. J Assoc Physicians India 1998; 46:424-6.
36. Greco TP, Conti-Kelly AM, Greco T, Doyle R, Matsuura E, Anthony JR, *et al*. Newer Antiphospholipid Antibodies Predict Adverse Outcomes in Patients With Acute Coronary Syndrome. Am J ClinPathol. 2009 Oct 1;132(4):613–20.
37. Nazarova M, Stanislavchuk M, Burdeina L. AB0602 Antiphospholipid syndrome components in patients with coronary heart disease. Annals of the Rheumatic Diseases. 2018 Jun 1;77(Suppl 2):1452–1452.
38. Desanctis. Clinical manifestations of coronary artery disease: Chest pain in women. In: Wenger NK, Speroff L, Packard B, eds. Cardiovascular health and disease in women. Greenwich Conn: Le Jacq communications, 1993:67-72.
39. Yavagal ST, Rangarajan R, Prabavathi, Chinnaiah D *Et al*. Clinical profile of myocardial infarction in Indian women(Abstr). Indian Heart J 1988; 40:359.
40. Chatterjee SS, Bannerji A, Dutta S, Guha S, Mazumder B, Sanyal R, Maity AK and Kar CC. Risk factors of myocardial infarction in Indian women. Indian Heart J 1987; 32:57.
41. Dave TH, Wasir HS. Profile of coronary artery disease in women; Correlation of clinical, non-invasive and coronary angiographic findings. Indian Heart J 1991;43(1):25-29.
42. Stone GW, Grines CL, Browne KF, Marco J, Rothumbaum D, O'Keefe J. *et al*. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary angioplasty for acute myocardial infarction. Am J Cardiol 1995; 759:87-92.
43. Babu BR, Rao Jv, Subramanyam G. Coronary heart disease in women- With special reference to young women. J AssocPhys India 1984; 32:48.
44. Hochman JS, Tamis JE, Thompson TD. Sex, clinical presentation andoutcome in patients with acute coronary syndromes. N Engl J Med 1999; 341:226-232.
45. Culic V, Eterovic D, Miric D, Sillic D, Symptom presentation of acute myocardial infarction: Influence of sex, age and risk factors. Am Heart J 2002:144:1012-17.

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