

THE DEMOGRAPHIC PROFILE, CLINICAL PRESENTATION & ANGIOGRAPHIC PREVALENCE AND PATTERN OF CORONARY ARTERY DISEASE IN WOMEN UNDERGOING CORONARY ANGIOGRAPHY.

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ABSTRACT

Objectives: The aim was to define the demographic profile, clinical presentation and angiographic prevalence and pattern of coronary artery disease (CAD) in women undergoing coronary angiography.

Data Sources: Medline databases (Pub Med, Circulation, American Heart Journal, British Medical journal and Science Direct) and also materials available in the Internet. The search was performed in the electronic databases from 2013 to 2017.

Study Selection: The initial search presented 150 articles of which 25 met the inclusion criteria. The articles studied the demographic Profile, clinical Presentation of CAD in women and also studied angiographic prevalence and pattern of CAD in women.

Data Extraction: If the articles did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and defined assessment measures.

Data Synthesis: Comparisons were made by structured review with the results tabulated.

Findings: In total 25 potentially relevant publications were included. The articles discussed the characteristics and risk factors attributed to CAD in Women, and also studied angiographic prevalence and pattern of CAD in women.

Conclusion: cardiovascular risk factors are highly prevalent among women and the combination of risk factors is common. Interventions to minimize CAD in our population are needed.

Key words: Coronary Artery Disease, Risk Factors, Chest Pain, Coronary Angiography, Women.

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INTRODUCTION

Since 1997, awareness of women recognizing heart disease as the leading cause of death has mildly increased from 37% to 54% in 2009^[1]. It is now estimated that 1 of 2 women will die of heart disease or stroke in USA, compared with 1 in 25 women will die with breast cancer^[2-4]. In Europe Cardiovascular disease kills a higher percentage of women (55%) than men (45%)^[5], due to sudden cardiac death prior to hospital arrival compared with men^[6,7].

But there are not many studies describing the presence of CAD in women undergoing coronary angiography and its pattern and distribution. During the past years, several studies reported gender difference in the epidemiology, clinical manifestation, diagnosis, management and prevention of CAD^[8], and a greater mortality rate was noted in women^[9,10]. Women with ischemic symptoms are less likely than men to be

referred for coronary angiography and vascularization procedure and are diagnosed and treated at later stage, which results in a worse prognosis and increase mortality^[11-14]. According to Framingham study, women have more frequent, episodes of angina, higher rate of hospitalization, high prevalence of myocardial infarction mortality, and higher rate of heart failure^[15, 16]. Many studies have shown that women tend to differ in their presents symptoms. They have more atypical symptoms than male, which makes the diagnosis more difficult, with higher incidence of normal coronary arteries in catheterization procedure^[17]. However, non-cardiac reasons for chest discomfort should be evaluated only after coronary disease has been ruled out^[18]. The rate of CAD increases as the number of risk factors increases. Women with two or more risk factors have more prevalence of CAD compared with

women without risk factors (50.2%, 8.2%) respectively ^[19].

MATERIALS AND METHODS

Search Strategy: We reviewed papers on the clinical presentation of CAD in women, and then we reviewed papers about the major risk factors of CAD in women, and also on angiographic prevalence and pattern of CAD in women, from Medline databases which are (Pub Med, Circulation, American Heart Journal, British Medical journal and Science Direct) and also materials available in the Internet. The search was performed in the electronic databases from 2013 to 2017.

Study Selection: All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria:

Inclusion criteria of the published studies:

- Published in English language.
- Published in peer-reviewed journals.
- Focused on CAD in women.
- Discussed the clinical presentation, risk factors of CAD in women and also the angiographic prevalence and pattern of CAD in women.

Data Extraction: If the studies did not fulfill the above criteria, they were excluded.

Quality Assessment: The quality of all the studies was assessed. Important factors included, study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, and adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

Data Synthesis: A structured systematic review was performed with the results tabulated.

RESULTS

A total of 25 studies were included in the review as they were deemed eligible by fulfilling the inclusion criteria. Studies discussed the clinical presentation, risk factors of CAD in women and also the angiographic prevalence and pattern of CAD in women.

The major risk factors of CAD in women:

Regarding menopause: 2 review articles ^[20, 21] clarified that although healthy premenopausal women are largely protected from cardiovascular disease, its prevalence rapidly rises after menopause. 1 prospective study ^[22] clarified that estrogen has an anti-inflammatory effect on atherosclerotic plaques.

1 multi-center, longitudinal cohort study ^[23] clarified that early menopause is positively associated with coronary heart disease, independent of traditional cardiovascular disease risk factors.

Regarding diabetes mellitus: 1 meta-analysis of prospective cohort studies ^[24] clarified that the relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men. 1 prospective study ^[25] clarified that women with diabetes have a greater than 3 fold increase in CAD risk than non-diabetic women.

1 retrospective observational study ^[26] clarified that age and diabetes are working independently on development of CAD in women.

Another meta-analysis of prospective cohort studies ^[27] clarified that though young and middle-aged women are less likely to develop CAD in the absence of diabetes, the presence of diabetes equalizes the risk by sex.

Regarding triglyceride, 1 prospective study ^[28] clarified that high levels of triglyceride are a significant risk factor of cardiovascular disease in both sexes, but more for women.

Regarding age, 1 prospective study ^[29] clarified that advancing age is a risk factor of CAD in women.

1 review article ^[30] clarified that the incidence of CAD was markedly lower in women <60 years of age than in older women. After 60 years of age, the rate of CAD increased and reached the rate seen among men by the 8th decade of life.

Regarding hypertension, 1 review article ^[31] clarified that prevalence of hypertension increase with age and reach 65% in women with age >65 years and confers a fourfold risk of CAD in females versus threefold in males.

The clinical presentation of CAD in women:

2 review articles ^[32, 33] and 1 multicenter prospective study ^[34] clarified that the most common presentation of obstructive coronary heart for women is atypical symptoms such as dyspnea, palpitation, weakness, indigestion, and chest pain as a feeling of fullness.

3 comparative prospective studies ^[35, 36, and 37] clarified that ischemic heart disease occurs predominantly as chest angina in women, whereas in men it does so in the form of acute myocardial infarction and sudden death. And women are more likely to have unstable angina than enzyme- or ECG-documented acute myocardial infarction; among those with myocardial infarction, fewer women than men had ECG-ST elevation myocardial infarction.

The prevalence and pattern of CAD in women:

1 review article ^[38] and 2 retrospective studies ^[39,40] clarified that among patients who were referred for chest pain and subsequently underwent angiography, a diagnosis of normal coronary arteries was more common in women than men.

1 multicenter and randomized controlled clinical trial ^[41] demonstrate that 50% of women undergoing coronary angiography for chest pain had either minimal or normal coronary artery narrowing.

1 comparative study ^[42] clarified that the diagnosis of coronary micro-vascular dysfunction should be considered in women with chest pain not attributable to obstructive CAD.

1 retrospective study ^[43] clarified more prevalence of single vessel disease in women and left anterior descending artery(LAD) was the most common vessel involved followed by almost equal prevalence of left circumflex artery(LCX) and right coronary artery(RCA).Left main artery (LMA) was the least affected vessel.

Another retrospective study ^[44] showed single vessel disease (SVD) in 15.8 percent, double vessel disease (DVD) in 12.9 percent, triple vessel disease (TVD) in 39.6 percent and normal coronary arteries in 30.7 percent.

1 retrospective study ^[26] studied the relationship between the major risk factors and number of vessels disease and the relationship between number of stenotic vessels and the clinical presentation.

Table (1): The major risk factors of CAD in women:

Study	Type	Outcomes
Barrett et al.,2013 (20)	Review Article	Although healthy premenopausal women are largely protected from cardiovascular disease, its prevalence rapidly rises after menopause.
Rosano et al.,2009 (21)	Review Article	The menopause compounds many traditional CAD risk factors, including changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction and vascular inflammation.
Burke et al., 2001 (22)	Prospective Study	Estrogen has an anti-inflammatory effect on atherosclerotic plaques, resulting in plaque stabilization.
Wellons M et al., 2012 (23)	Multi-center, Longitudinal Cohort Study	Early menopause is positively associated with coronary heart disease, independent of traditional cardiovascular disease risk factors.
Huxley et al.,2006 (24)	Meta-analysis of Prospective Cohort Studies	The relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men.
Spencer et al.,2008 (25)	Prospective Cohort Study	Women with diabetes have a greater than 3 fold increase in CAD risk than non-diabetic women.
Yehia A et al.,2015 (26)	Retrospective Observational	Age and diabetes are working independently on development of CAD in women.

Study	Type	Outcomes
	Study	
Rita et al.,2014 (27)	Meta-analysis of Prospective Cohort Studies	Though young and middle-aged women are less likely to develop CAD in the absence of diabetes, the presence of diabetes equalizes the risk by sex.
Reardon et al.,1985 (28)	Prospective Study	High levels of triglyceride are a significant risk factor of cardiovascular disease in both sexes, but more for women.
Wenger et al.,1993 (29)	Prospective Study	Advancing age is a risk factor of CAD in women.
Blum A et al., 2009 (30)	Review Article	The incidence of CAD was markedly lower in women <60 years of age than in older women. After 60 years of age, the rate of CAD increased and reached the rate seen among men by the 8th decade of life.
Wenger et al.,2003 (31)	Review Article	Prevalence of hypertension increase with age and reach 65% in women with age >65 years and confers a fourfold risk of CAD in females versus threefold in males.

CAD: coronary artery disease, CVD: cardiovascular disease.

Table 2: The clinical presentation of CAD in women:

Study	Type	Outcomes
Shawet al.,2006(WISE) Study part I(32)	Review Article	Most common presentation of obstructive coronary heart for women is atypical symptoms such as dyspnea, palpitation, weakness, indigestion, and chest pain as a feeling of fullness.
Leuzziet al.,2010 (33)	Review Article	Symptoms do not help physicians in differential diagnosis of chest pain in women; indeed the most common presentation of obstructive CAD in women is atypical symptoms.
Devonet al.,2008 (34)	Multicenter Prospective Study	Regardless of clinical diagnostic category, women reported significantly more indigestion (beta = 0.25; CI = 0.01-0.49), palpitations (beta = 0.31; CI = 0.06-0.56), nausea (beta = 0.37; CI = 0.10-0.65), numbness in the hands (beta = 0.29; CI = 0.02-0.57), and unusual fatigue (beta = 0.60; CI = 0.27-0.93) than men reported. Differences between men and women in dizziness, weakness, and new-onset cough did differ by diagnosis. Reports of chest pain did not differ between men and women.
Kannel WB et al.,2002 (35)	Comparative Prospective Study	CAD initially presented as chest angina in 65% of women and in 35% of men, whereas infarction or sudden death were the first manifestation in 37% of women and 63% of men.
Bowker TJ et al.,2000 (36)	Comparative Prospective Study	In a sample of over 1000 patients <70 years old, 42% presented acute myocardial infarction, with a significantly greater proportion of men than women (45 vs. 38%; $P=.02$).
Hochman JSet al.,1999 (37)	Comparative Prospective Study	Presentation with ST-segment elevation was significantly lower in women compared to men(27.2 vs. 37%; $P<.001$).

CAD: coronary artery disease, CI: confidence interval

Table 3: The prevalence and pattern of CAD in women:

Study	Type	Outcomes
Parsyan al.,2012 (38)	Aet Review Article	Women who were peri-or postmenopausal were found to have an increased risk of angina with no obstructive CAD.
Humphries KH et al.,2008 (39)	Retrospective Study	Study of 32,856 patients presenting for their first cardiac catheterization with suspected ischemic heart disease, 23.3% of women versus 7.1% of men were found to have normal coronaries following angiography.
Sullivan AK et al.,1994 (40)	Retrospective Study	Among 886 patients who were referred for chest pain and subsequently underwent angiography, a diagnosis of normal coronary arteries was more than five times more common in women than men (41% versus 8%)
Kennedy et al.,1985 (41)	Multicenter and Randomized Controlled clinical trial	50% of women undergoing coronary angiography for chest pain had either minimal or normal coronary artery narrowing.
Reis et al.,2001(42)	Comparative Study	The diagnosis of coronary micro-vascular dysfunction should be considered in women with chest pain not attributable to obstructive CAD.
Ezhumalai B et al.,2014 (43)	Retrospective Study	More prevalence of SVD in women and LAD was the most common vessel involved followed by almost equal prevalence of LCX and RCA. LMA was the least affected vessel.
Dave TH, et al.,1991 (44)	Retrospective Study	Coronary angiography showed SVD in 15.8 percent, DVD in 12.9 percent, triple vessel disease TVD in 39.6 percent and normal coronary arteries in 30.7 percent.
Yehia A et al.,2015 (26)	Retrospective Observational Study	Patients with no risk factors, had (4.5%) normal coronary, and (2.6%) SVD, however women with one risk factors had 17.9% normal coronaries (7.1%) SVD and (9.3%, 6.5%) DVD and TVD respectively. Also, when the number of risk factors increase the number of vessels disease increase. 65.6% of patients with atypical chest pain had normal coronaries; and only 2.6% had SVD. Study population had myocardial infarction, had high prevalence of coronary disease (25.3%, 33.9%, 30.6%) SVD, DVD, TVD respectively, and only 4.2% had normal coronaries. In other hand, patients with unstable angina had multi-vessels disease, and most of patients with chronic stable angina had SVD (28.6%),

CAD: coronary artery disease, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LMA: Left main artery, SVD: single vessel disease, DVD: double vessel disease, TVD: triple vessel disease.

DISCUSSION

Ischemic heart disease (IHD) is the biggest killer of women globally. IHD causes 8.6 million deaths among women annually, a third of all deaths in women worldwide. Every year more women than men die of

IHD. Women in low and middle income countries have worse situation than men, experiencing higher proportion of IHD deaths than men ^[45]. Women continue to be under represented in research on heart disease. Most of the studies conducted on IHD are based on

male population and whether we should implement the same guidelines on women counterparts is an unanswered question^[46]. With more data from Women's Ischemia Syndrome Evaluation Study (WISE), as well as other new studies during the past several years, an evolving knowledge regarding sex differences in IHD has emerged. Women and men with heart disease tend to differ in their presenting symptoms, access to investigations, treatment and overall prognosis^[47]. Women present with more atypical symptoms than men like back pain, shortness of breath, burning in the chest, nausea, or fatigue, which makes the diagnosis more difficult. The clinical presentation of IHD differs between women and men. Compared with men, women are more likely to develop angina as their first manifestation of IHD (47% versus 32%) and less likely to present with an acute myocardial infarction; (6% versus 10%)^[48]. This presentation pattern, which was initially reported in the USA in the 1980s by the Framingham Heart Study investigators,^[49] was confirmed by the results of a 2008 meta-analysis of data from 31 countries showing that women have, on average, a 20% higher rate of angina than men, irrespective of their rate of coronary death^[50]. In the setting of acute coronary syndrome (ACS), women and men have different clinical profiles and presentation, with fewer women than men presenting with ST-segment elevation myocardial infarction, but more presenting with unstable angina^[51,52].

Presence of chest pain, particularly if 'typical' in character, is a predictor of obstructive coronary artery disease CAD in both women and men, although fewer women than men have obstructive CAD in each category of chest pain (typical, atypical, or non-angina chest pain)^[53].

Physicians tend to underestimate cardiovascular risk in women, which can lead to missed or delayed diagnoses of IHD^[54,55]. Part of the problem is that the diagnosis of IHD in women is hampered by difficulties arising from sex-related differences in the

prevalence and clinical manifestations of this disease and its risk factors^[56].

Risk factors for IHD vary between males and females^[57]. Diabetes mellitus is a stronger IHD risk factor in women than in men. Diabetes carries a greater risk in females, completely eliminating the "female advantage"^[58]. Diabetes removes the estrogens protective effects and eliminates the normal sex difference in the prevalence of IHD^[59]. Diabetes equalizes the risk of IHD between premenopausal diabetic women and non-diabetic men of same age^[60].

Diabetes is associated with other IHD risk factors like obesity, dyslipidemia, and hypertension and insulin resistance. Lastly diabetes is associated with various coagulation abnormalities like endothelial dysfunction and platelet abnormalities, additional contributors to IHD^[58].

Hypertension confers a fourfold risk of IHD in females versus threefold in males^[31]. Hypertension is strongly correlated with obesity and is six fold higher in females with Body mass index (BMI) more than 30 in comparison to females with less than 20 BMI. Weight reduction of 10 kg decreases systolic blood pressure by six mmHg and diastolic by three mmHg in hypertensive females^[31]. Elevated total cholesterol and low density lipoprotein (LDL) is important risk factor for IHD in men, but in women low high density lipoprotein (HDL) and high triglycerides are important risk factors^[61-63].

Data from Nurses' health study revealed that mortality due to IHD in obese women was fourfold higher than lean ones^[64]. In premenopausal women endogenous estrogen provides protection from IHD. Additionally, estrogen enhances elasticity of vessel wall, reduces hypertrophy of cells, and has anti-inflammatory and anti-oxidative properties^[32]. In females increasing level of physical activity and physical fitness will improve their cardiovascular risk profile^[65]. Protection from IHD in younger women is due to endogenous estrogen. At the age of 60, the level of atherogenic lipids increase and risk of IHD doubles for women^[66].

Globally, there has been a substantial rise in the proportion of women undergoing coronary angiography over the last few years. The reasons for this evolutionary change may be multifactorial. As a preliminary step in the process of discerning these changes, the clinical and angiographic profiles of women undergoing coronary angiography must be understood. There are not many studies describing the prevalence and pattern of CAD in women undergoing coronary angiography⁽⁶⁷⁾.

Hence, uncertainty thrives with regard to the angiographic prevalence and pattern of CAD in women. Stenosis of LMA is a relatively uncommon but significant cause of increased morbidity and mortality among patients with CAD⁽⁶⁷⁾. The magnitude of problem imposed by “left main disease” (LMD), though well established in men, has not been explored in women. Moreover the strategy of stent deployment (provisional side branch stenting strategy or two stent strategy) in the interventions of LMA depends on the pattern of CAD. Hence, a study about angiographic prevalence and pattern of CAD especially LMD in women will definitely open up new avenues for the better understanding of the strategy for percutaneous coronary intervention⁽⁶⁸⁾.

Conclusion:

Women with documented coronaries disease tend to be older, have higher systolic blood pressure, serum level of triglyceride. (59.7%) of them are menopause with higher prevalence of hypertension and diabetes. Significant positive association is found in women with myocardial infarction, unstable angina, stable angina and presence of obstructive coronary artery disease in opposite women presented with atypical chest pain have high prevalence of normal coronaries. Most common presentation of obstructive coronary heart for women is atypical symptoms such as dyspnea, palpitation, weakness, indigestion, and chest pain as a feeling of fullness. Among patients who were referred for chest pain and subsequently underwent angiography, a diagnosis of normal coronary arteries was

more common in women than men. More prevalence of SVD in women and LAD was the most common vessel involved.

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