Review Coronary Heart Disease in Women

Dr Prabha Chapagain Koirala [1], , Dr Rajendra Bhandari[1]

[1] Department of Cardiology, National Academy of Medical Sciences, Bir Hospital, Mahaboudha, Kathmandu, Nepal,

Abstract:

Coronary heart disease is increasing in women all over the world. Due to the perception that women are less likely to have coronary heart disease there is still delay in diagnosis and treatment of women with coronary artery disease and acute coronary syndrome. Few coronary heart disease risk factors such as diabetes, dyslipidemia and obesity are more prominent in female as compared to male. There is gender wise differences in clinical presentation, pathophysiological mechanism and outcomes of acute coronary syndrome in women. Non- obstructive coronary artery disease is common in women. Microvascular dysfunction, coronary vasospasm, Spontaneous coronary artery dissection, plaque erosion is common pathophysiological mechanism of acute coronary syndrome in women. This article reviews the coronary artery disease risk factors. clinical presentation, pathophysiological mechanism and outcome of acute coronary syndrome and coronary artery disease in women.

Conclusion:

As recent evidences reveal that there is sex differences in coronary artery disease, women with coronary artery disease needs special guideline and strategy for diagnosis, management and prevention of coronary artery disease. Clinical trials focused on women's health and adequate representation of women in clinical trials is the need of today.

Key words: Coronary artery disease, cardiac risk factors, acute coronary syndrome

---

Introduction:

Cardiovascular diseases (CVD) account for the major cause of death worldwide. In 2019, 17.9 million people were estimated to have died from CVDs, representing a total of 35% death globally, of which 85% were caused by heart attack and stroke.[1] Coronary heart disease (CHD) stands as a major cause of death among women.

About 80% of women of age 40 to 60 are found to have one or more cardiac risk factors, increasing their likelihood for later on developing CHD. [3]

As compared to men, certain medical conditions occur more commonly in women that increase their risk of coronary heart disease, such as: anemia**,** early menopause (before age 40), history of gestational diabetes, preeclampsia, eclampsia , hormonal birth control, inflammatory **a**nd autoimmune diseases, lack of physical activities, metabolic syndrome and mental health problems**,** such as stress, anxiety and, depression.[3]

Females are said to be 'protected' against cardiovascular disease; this misconception has led to a scenario where the risk of CVD in women is often underestimated and, when CVDs do occur, women are found to receive less aggressive treatment due to the variable clinical presentation of CVD in women. Female representation in clinical trials is also on the lower side, thereby creating a gap in gender specific evidence .[4]

Coronary Artery Disease Risk Factors:

The concept of "risk factors" in coronary heart disease was first created by the Framingham heart study (FHS), which published its findings in 1957. FHS demonstrated the epidemiologic relations of cigarette smoking, blood pressure, and cholesterol levels to the incidence of coronary artery disease (CAD). [5,6]

Coronary risk factors are divided in two broad categories: non-modifiable and modifiable risk factors. Non-modifiable risk factors include: age, gender, ethnicity, and family history of CAD. Modifiable risk factors include hypertension, hyperlipidemia, diabetes mellitus (DM), obesity, smoking, poor diet, sedentary lifestyle, and stress. [5, 6 ,7 ,8]

The INTERHEART study is a global case–control study including 27098 participants from 52 countries, out of whom 6787 were women (including about 3000 cases). It is one of the largest studies of myocardial infarction (MI) risk factors in women. It included women from South Asia and other developing countries. It has demonstrated that although men and women have similar risk factors for coronary heart disease, certain risk factors are more prominent in women. These include tobacco abuse, type 2 DM**,** depression, and other psychosocial risk factors**.** According to this study there were nine easily measurable and modifiable risk factors that could explain more than 90 per cent of the risk of a heart attack globally in all regions and major ethnic groups of the world. These modifiable risk factors are smoking, hypertension, DM, waist to-hip ratio, dietary patterns, physical activity, alcohol consumption, plasma apo-lipoproteins, and psychosocial factors which account for 96% of the population-attributable risk of MI in women. Among women, ApoB/A levels, current smoking, hypertension, and diabetes were more strongly associated with MI in younger compared to older women. [9]

Similarly, in another recent study done in India by Iyengar S.S et al. where 997(72% men and 28% female) young patients (men <55, women <65) presenting with ACS or stable ischemic heart disease (IHD) at 22 centers across India were recruited; women, as compared to men, had greater prevalence of diabetes (62.1 vs 37.1%, $p < 0.001$), hypertension (72.1 vs 40.3%, $p < 0.0001$) and overweight/obesity (60.1 vs 35.2%, $p < 0.0001$), whereas men had greater prevalence of smoking/tobacco use (52.7 vs 3.2%, $p < 0.0001$).[10]

Other studies done in India, in women with acute coronary syndrome had also shown that the prominent CAD risk factors were hypertension, diabetes, smoking and dyslipidemia with high levels of total cholesterol, triglycerides along with reduced high density lipid (HDL).[11, 12]

Another study was done by Kudenchek PJ et al, which compared the signs and symptoms , treatment, and outcome of 1,097 patients (851 men and 246 women) with confirmed acute myocardial infarction from the Myocardial Infarction Triage and Intervention (MITI) Project Registry, In that study Women were older than men and had a higher prevalence of known cardiovascular risk factors and women did not receive adequate treatment . Outcome was also less favorable for women**.** [13]

Other studies have also shown that on comparing men and women; women were older than men and had a higher prevalence of known cardiovascular risk factors**.** [14,15]

According to Mehta SL et al black women would have a higher prevalence of acute MI compared with other women, including higher rates of sudden cardiac death. Asian Indian women would have higher mortality rates, which might be associated with higher rates of cardiovascular disease (CVD) risk factors. [16]

The EUROASPIRE IV, a cross-sectional survey on hospitalized patients with coronary artery disease (n=7,998; ages of 18–80 years) including centers from 24 European countries. demonstrated that prevalence of multiple cardiovascular risk factors (3 or more from 5 risk factors including smoking, obesity, high blood pressure, high LDL cholesterol and diabetes) was significantly higher in female patients than in male patients .[17]

Smoking:

Smoking is one of the most important preventable risk factor for the development of coronary heart disease (CHD) among men and women. Cigarette smoking is the most important leading cause of MI in women. Smoking increases both men's and women's risk of a major heart attack at all ages, but especially women smokers under 50 years old have a significantly higher increased risk compared to men.[18]

In the INTERHEART study, current smoking was more strongly associated with MI in younger women compared to older women.[9]

At younger ages (<50 years) smoking is more deleterious in women than in men. As compared to male smoker, first acute myocardial infarction (AMI) occurred significantly more prematurely in women smoker, the reason may be tobacco smoke exerting anti-estrogenic effect. [19, 20]

Hypertension:

High blood pressure (HTN) is a major risk factor for heart disease. Hypertension is a major risk factor for MI in women. More than 56 million women in the United States (44.3%) have high blood pressure or are taking antihypertensive drugs.[21]

In INTERHEART study, hypertension was more strongly associated with MI in women compared with men and the Population attributable risk (PAR)**: (**35.8 vs. 19.5%) was significantly greater among women compared to men.[9]

The 10-year follow-up study with 13,740 Dutch women, showed that elevated systolic blood pressure was associated with increased rates of cardiovascular mortality for women. A very high increase in cardiovascular mortality was observed among hypertensive diabetic women. [22]

Obesity and Dyslipidemia:

Obesity is a major risk factor for type 2 diabetes, and dyslipidemia is also closely associated with diabetes. The lipid accumulation product (LAP), an index calculated by using levels of serum triglycerides and waist circumference, has been reported to be a good discriminator for diabetes.[23]

Obesity leads to increase in incident of cardiovascular disease risk factors, such as dyslipidemia, type 2 diabetes and hypertension; it also plays major role in the development of the cardiovascular disease and cardiovascular disease mortality independently of other cardiovascular risk factors. More recent data reveals abdominal obesity as a cardiovascular disease risk marker that is independent of body mass index. [24]

The risks of developing CAD increases by 40% with every 10 cm rise in waist circumference, with an odds ratio of 1.04 (95% CI: 1.01-1.07, P = 0.013) for a 1 cm increment. [25]

Higher waist hip ratio (WHR) and greater waist circumference were independently associated with a significantly increased age-adjusted risk of CHD in women. It was observed that women with a WHR of 0.88 or higher had a relative risk (RR) of 3.25 (95% confidence interval [CI], 1.78-5.95) for CHD compared with women with a WHR of less than 0.72.[26]

Data from the Nurse's Health Initiative study showed that the incidence of IHD among women who followed healthy lifestyle and had lower BMI was significantly lower compared with women who had increased adiposity, high cholesterol levels, and lack of regular physical activities. [27]

Besides this, central obesity corresponding to increased waist circumference is an important component of the insulin resistance; hyperinsulinemia syndrome and has been found to be more frequent in persons of Indian origin. Central/Abdominal obesity is generally regarded as a more important predictor of ischemic heart disease than generalized obesity.[9]

Reduced HDL cholesterol and high triglyceride levels are powerful risk factors for CHD in women. Among 32826 postmenopausal women from the Nurses' Health Study, high-density lipoprotein cholesterol was the lipid parameter that best discriminated risk of CHD. [28]

Obesity is one of the major risk factor for CAD in Indian women. Studies done in India have shown that 40 to 60% Indian women had obesity.[10, 11,] The result of INTERHEART Study showed that metabolic syndrome was a significant risk factor for acute MI, in both women and men, from all regions and ethnic groups. similar to diabetes or hypertension alone.[29]

Diabetes Mellitus:

Diabetes Mellitus (DM) is an important cardiovascular risk factor. DM is a powerful risk factor in young women, increasing their risk of CAD, including ACS, by 4- to 5-fold. [30] According to INTERHEART STUDY, among women, diabetes was more strongly associated with MI in younger compared to older women.[9]
According to the Rancho Bernardo study, the relative hazard of ischemic heart disease death in diabetics vs nondiabetics was 1.8 in men and 3.3 in women, after, adjusting for age, systolic blood pressure, cholesterol, body mass index, and cigarette smoking using the Cox regression model.[31]

The meta analysis of 64 cohorts, including about 900,000 individuals and over 28,000 incident CHD events, demonstrates that women with diabetes have more than 40% greater risk of incident CHD as compared with men with diabetes. [32]

Menopause:

Menopause is an important cardiac risk factor. Due to hormonal changes the risk of development of coronary heart disease is increased in women after menopause.[33]

The reason for the increase in the risk of coronary artery disease in post-menopausal women is that natural menopause has an unfavorable effect on lipid metabolism.[34] Menopause-related hot flashes and night sweats have been associated to a greater risk for high blood pressure and other cardiovascular risk factors in women. Depression which is common during the menopause transition is strongly associated to higher cardiovascular disease risk in women. [35]

Epidemiological evidence has shown that menopausal transition is associated with a higher prevalence of CVD risk factors, such as central adiposity, atherogenic dyslipidemia, glucose intolerance, arterial hypertension (AH) and non-alcoholic fatty liver disease (NAFLD), compared with premenopausal status.[36]

The pan European case control study revealed that early and surgical menopause was associated with higher CHD risk. Similarly, another meta-analysis also had shown that women with early menopause i.e. before age of 45 years had a 50% increased risk of coronary heart disease.[37]

A cross-sectional study of ninety-six women which was conducted to examine the effect of menopause and hormone replacement therapy (HRT) on plasma lipids, lipoproteins and oxidation of low density lipoproteins showed that postmenopausal women not taking replacement hormones had significantly higher plasma cholesterol, low density lipoprotein (LDL) cholesterol and lipoprotein[a] (Lp[a]) levels compared to premenopausal women or postmenopausal women on HRT These results confirm the effect of menopause and exogenous hormones on plasma lipids and lipoproteins, LDL receptor.[38]

Several studies have shown that apart from the traditional cardiac risk factors, even the levels of novel cardiovascular risk factors such as markers of insulin resistance, inflammation, activated coagulation and endothelial dysfunction are significantly greater in women than in men.[39, 40, 41]

The pathophysiology of ACS in women:

The pathophysiology of acute coronary syndrome (ACS) may also differ between men and women. Plaque erosion is the most frequent cause of ACS in women, while in male it is plaque rupture. Plaque erosion is seen in about one third of intravascular imaging of angiographically normal vessel in women with ACS.[42]

Smoking and female gender are strong risk factors for endothelial erosion. Multiple mechanisms may contribute to endothelial erosion, including endothelial dysfunction,

Toll-like receptors (TLR) signaling, leukocyte activation and modification of sub-endothelial matrix by endothelial or smooth muscle cells, which may trigger loss of adhesion to the extracellular matrix or endothelial apoptosis.[42]

Spontaneous coronary artery dissection (SCAD), a rare cause of ACS, occurs mostly in young women.[43] In a prospective cohort of patients with SCAD, more than 90% of patients were female . Hypertension was found to increase the risk of recurrent SCAD. [43]

Spontaneous coronary artery dissection (SCAD) is an important cause of myocardial infarction accruing during pregnancy and post-partum periods. [44,45]

As compared to men, women have lower burden of obstructive coronary artery disease but more symptoms, ischemia, and adverse outcomes, which is due to abnormal coronary reactivity that includes microvascular dysfunction. [46] Microvascular dysfunctions are common is common in women with ACS.[47, 48] According to Reis et al. coronary microvascular dysfunction can be identified in approximately half of women with chest pain in the absence of obstructive CAD.[48] When women with chest pain do not have obstructive CAD, the diagnoses of coronary microvascular dysfunction should be considered.[48, 49] Another study also showed that about two-thirds of women with non-obstructive coronary artery disease had evidence of microvascular dysfunction.[47]

There are different causes for coronary microvascular dysfunction (CMD) such as epicardial abnormal vasomotion or endothelial microvascular dysfunction, atherosclerotic emboli or inflammation. [49 ,50] Contemporary data indicate that patients with signs and symptoms of ischemia and non-obstructive coronary artery disease (INOCA) often have coronary microvascular dysfunction (CMD) with elevated risk for adverse outcomes.

Coronary vasospasm is also a common mechanism in women with non-obstructive lesions [51, 52]

MI with non-obstructive coronary arteries (MINOCA) occurs in 5–15% of patients presenting with acute ST-segment elevation MI or non-ST segment elevation MI. [53]

Clinical symptoms of acute coronary disease in women:

Our review reveals that the most prominent symptom in both males and females during MI is chest pain. Studies have demonstrated that there are differences in symptom presentation associated with coronary artery disease between men and women. Chest pain is similar in both men and women however atypical symptoms such as nausea, dyspnea palpitations and indigestion are more prominent in women. [14 ,54] Chest pain was the most frequently reported symptom in women (70%) and men (71%).[54] Some study revealed that approximately 90% of women and men with a myocardial infarction (MI) experience chest pain as their main presenting symptom However, women often experience more other accompanying symptoms along with the chest pain.[55, 56]

Another study also revealed that, chest pain was the predominant symptom in both sexes; however, women reported a greater number of symptoms than men. The most common symptoms except chest pain were weakness, feeling hot, shortness of breath, cold sweats, and pain in the left arm or shoulder.in both sexes regardless of ACS type. [57]

The systematic review and meta-analysis of 27 studies including >1 million patients shows that, there is sex differences in symptom presentation in patients with confirmed ACS, however some symptoms do overlap. According to this meta-analysis, most common symptoms for both sexes were, chest pain, diaphoresis, shortness of breath, left arm and left shoulder pain, and nausea or vomiting. But women with ACS have higher odds of presenting with pain between the shoulder blades, nausea or vomiting and shortness of breath compared with men.[58]

Coronary Angiographic Findings in Women:

There is differences in findings of coronary artery disease in between men and women.
Women have low rates of anatomical or obstructive coronary artery disease as compared to men.[46] It was observed that a diagnosis of normal coronary arteries was five times more common in women than men.[59] Other studies also showed that diagnosis of normal coronary arteries was present in (12-15%) of women.[14, 60]

It was observed that the most common presentation of CAD in women was unstable angina or non-ST segment elevation MI while in men it was ST elevation MI**.** Most common coronary angiography finding in women was single vessel disease, followed by triple vessel disease [60]

In the study carried out by Chiha .J et al. there was a marked difference in coronary artery disease severity and burden between females and males suspected of angina. Women compared to men without infarction had a lower burden of CAD with up to 50% having normal coronary arteries in the 30–44-years group and 40% in the 45–59-years group.[61]

In the analysis of data of Korean women 's chest pain registry, it was found that the prevalence of obstructive CAD was significantly higher in men than in women (37.0% vs. 28.4%, $P < 0.001$). Men had a higher prevalence **of** Left Main disease (10.3% vs. 3.5%, $P < 0.001$) and three-vessel disease (16.1% vs. 9.5%, $P = 0.007$) compared to women.[62]

,

Treatment outcome and mortality of CAD in women:

Although a lot progress and development have been made in the diagnosis and management of coronary artery disease and acute coronary syndrome, there exists sex differences in the diagnosis, management and outcome of coronary artery disease and ACS in women.

Even after diagnosis, women are less likely than men to be referred for coronary angiography, percutaneous intervention, and fibrinolysis. Women receive less intensive medical therapy both during and after an ACS event. It has been observed that post-ACS outcomes are poorer in women than in men. [63] It is found that there is persistent knowledge gap with regard to optimal management of female ACS patients.[64]

The condition of management of ACS is still inadequate for women everywhere and. the situation seems to be same in developed countries also More than 1.2 million percutaneous coronary interventions are performed annually in the United States, with only an estimated 33% performed in women, despite the established benefits of percutaneous coronary intervention and adjunctive pharmacotherapy.[65]

The studies done in Europe have also shown that women were treated differently as compared to men. Fewer women with a positive history of ACS received revascularization.[66, 67]

In another study done in Australia showed that women received less invasive management revascularization and preventive medication at discharge [68]

Not only women receive less evidence-based medical care than men but have higher rates of death after acute myocardial infarction (AMI). As compared to men, after myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting, women have poorer prognosis and outcome. Mortality after first MI is higher for women than men. Women have higher risk of recurrent MI, heart failure or death after first MI.[4]

Women had more complications than men during hospitalization and a higher mortality rate at 30 days (6.0 percent vs. 4.0 percent, P<0.001). [15] The risk for hospital mortality in women was almost twice that for men (odds ratio 1.95 [1.01 to 3.8]).[13]

Similarly, another study revealed that after myocardial infarction, younger women, had higher rates of death during hospitalization than men of the same age. The younger the age of the patient, the higher the risk of death among women relative to men. [69]

After adjustment for age and extent of disease, women were more likely to have adverse outcomes (death, myocardial infarction, stroke and re hospitalization) at six months compared to men.[14]

The analysis of 10-year mortality data of the Women's Ischemia Syndrome Evaluation(WISE) study showed that women with non-obstructive lesions had higher mortality rates, and CAD risk factors such as dyslipidemia, hypertension, and T2 DM which played major role in mortality [70].

Conclusion:

There is difference in pathophysiology, clinical sign and symptoms, coronary angiography findings and outcomes in between male and female. Women are receiving less guideline directed therapy than men. Outcome of acute myocardial infarction is poorer in women. In this way we can say still there are a lot thing to do for the adequate management of female patients with coronary artery disease and acute coronary syndrome.

Reference:

1. World Health Organization ://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)'' Jun 11, 2021 world Health Organization. Cardiovascular diseases. Jun 11, 2021
2. World Health Organization .https://www.who.int/news/item/09-12-2020
3. Coronary Heart Disease - Women and Heart Disease . NHLBI . National Institutes of Health (.gov). https://www.nhlbi.nih.gov › health › women
4. Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J. 2010 Dec;18(12):598-602. doi: 10.1007/s12471-010-0841-y. PMID: 21301622; PMCID: PMC3018605.
5. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 2014 Mar 15;383(9921):999-1008. doi: 10.1016/S0140-6736(13)61752-3. Epub 2013 Sep 29. PMID: 24084292; PMCID: PMC4159698.
6. Hajar R. Risk Factors for Coronary Artery Disease: Historical Perspectives. Heart Views. 2017 Jul-Sep;18(3):109-114 doi: 10.4103/HEARTVIEWS.HEARTVIEWS_106_17. PMID: 29184622; PMCID: PMC5686931.
7. Jousilahti P, Laatikainen T, Peltonen M, Borodulin K, Männistö S, Jula A, Salomaa V, Harald K, Puska P, Vartiainen E. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. BMJ. 2016 Mar 1;352:i721. doi: 10.1136/bmj.i721. PMID: 26932978; PMCID: PMC4772739.
8. Pencina MJ, Navar AM, Wojdyla D, Sanchez RJ, Khan I, Elassal J, D'Agostino RB, Peterson ED, Sniderman AD. Quantifying Importance of Major Risk Factors for Coronary Heart Disease. Circulation. 2019 Mar 26;139(13):1603-1611. doi: 10.1161/CIRCULATIONAHA.117.031855. PMID: 30586759; PMCID: PMC6433489.
9. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al: INTERHEART Study . Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9. PMID: 15364185..
10. Iyengar SS, Gupta R, Ravi S, Thangam S, Alexander T, Manjunath CN,et al. Premature coronary artery disease in India: coronary artery disease in the young (CADY) registry. Indian Heart J. 2017 Mar-Apr;69(2):211-216. doi: 10.1016/j.ihj.2016.09.009. Epub 2016 Nov 30. PMID: 28460769; PMCID: PMC5414957.
11. Jain S, Sarkar NC, Sarkar P, Modi N, Tilkar M. Evaluation of Coronary Artery Status by Coronary Angiography after First Survival of Acute Myocardial Infarction. J Clin Diagn Res. 2015 Dec;9 (12):OC06-8. doi: 10.7860/JCDR/2015/16502.6887. Epub 2015 Dec 1

12. Sahni M , Kumar R, Thakur S, Bhardwaj R : Clinical profile, risk factors and short term outcome of acute myocardial infraction in females: A hospital based study. Heart India 2013; 1 (3) : 73-77. *DOI:* 10.4103/2321-449x.122780
13. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). Am J Cardiol. 1996 Jul 1;78(1):9-14. doi: 10.1016/s0002-9149(96)00218-4. PMID: 8712126.
14. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA, Eagle KA; Global Registry of Acute Coronary Events investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009 Jan;95(1):20-6. doi: 10.1136/hrt.2007.138537. Epub 2008 May 7. PMID: 18463200.
15. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med. 1999 Jul 22;341(4):226-32. doi: 10.1056/NEJM199907223410402. PMID: 10413734.
16. Mehta LS ,Beckie TM, DeVon HA, Grines C L et al. Acute Myocardial Infarction in Women:AScientific Statement From the American Heart Association. ; Circulation.Circulation. 2016 Mar 1;133(9):916-47. doi: 10.1161/CIR.0000000000000351
17. De Smedt D, De Bacquer D, De Sutter J, et al. The gender gap in risk factor control: Effects of age and education on the control of cardiovascular risk factors in male and female coronary patients. The EUROASPIRE IV study by the European Society of Cardiology. Int J Cardiol 2016;209:284-90. doi: 10.1016/j.ijcard.2016.02.015. Epub 2016 Feb 3. PMID: 26913370.
18. American College of Cardiology https://www.acc.org › press-releases › 2019/06/24 › Young Women Who Smoke Face Highest Risk of Major Heart Attack.
19. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998; 316:1043-7. doi: 10.1136/bmj.316.7137.1043. PMID: 9552903; PMCID: PMC28505.
20. Grundtvig M, Hagen TP, German M, Reikvam A. Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men. Eur J Cardiovasc Prev Rehab.2009;16:174-9. https://doi.org/10.1097/HJR.0b013e328325d7f0.
21. Centers for Disease Control and Prevention. Estimated Hypertension Prevalence, Treatment, and Control Estimates Among US Adults. Accessed Feb 24, 2022. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html.
22. van der Giezen AM, Schopman-Geurts van Kessel JG, Schouten EG, Slotboom BJ, Kok FJ, Collette HJ. Systolic blood pressure and cardiovascular mortality among 13,740 Dutch women. Prev Med. 1990 Jul;19(4):456-65. doi: 10.1016/0091-7435(90)90043-j. PMID: 2399226.
23. Kahn HS. The lipid accumulation product is better than BMI for identifying diabetes: a population-based comparison. Diabetes Care 2006 Jan;29(1):151-3. doi: 10.2337/diacare.29.1.151. PMID: 16373916.
24. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and Cardiovascular Disease: A Scientific Statement From the American

Heart Association. Circulation. 2021 May 25;143(21):e984-e1010. doi: 10.1161/CIR.0000000000000973. Epub 2021 Apr 22. PMID: 33882682; PMCID: PMC8493650.

25. Azab M, Al-Shudifat AE, Johannessen A, Al-Shdaifat A, Agraib LM, Tayyem RF. Are Risk Factors for Coronary Artery Disease Different in Persons With and Without Obesity? Metab Syndr Relat Disord. 2018 Oct;16(8):440-445. doi: 10.1089/met.2017.0152. Epub 2018 Aug 8. PMID: 30088947.

26. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE. Abdominal adiposity and coronary heart disease in women. JAMA. 1998 Dec 2;280(21):1843-8. doi: 10.1001/jama.280.21.1843. PMID: 9846779.

27. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000 Jul 6;343(1):16-22. doi: 10.1056/NEJM200007063430103. PMID: 10882764.

28. Shai I, Rimm EB, Hankinson SE, Curhan G, Manson JE, Rifai N, Stampfer MJ, Ma J. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: potential implications for clinical guidelines. Circulation. 2004;110:2824–2830. doi: 10.1161/01.CIR.0000146339.57154.9B.

29. Mente A, Yusuf S, Islam S, McQueen MJ, HC, Anand SS; INTERHEART Investigators. Metabolic syndrome and risk of acute myocardial infarction a casecontrol study of 26,903 subjects from 52 countries. J Am Coll Cardiol. 2010;55:2390–2398. doi: 10.1016/j.jacc.2009.12.053.

30. Kalyani RR, Lazo M, Ouyang P, Turkbey E, Chevalier K, Brancati F, Becker D, Vaidya D. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. Diabetes Care. 2014;37:830–838. doi: 10.2337/dc13-1755
31. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why Is Diabetes Mellitus a Stronger Risk Factor for Fatal Ischemic Heart Disease in Women Than in Men? The Rancho Bernardo Study. *JAMA.* 1991;265(5):627–631. doi:10.1001/jama.1991.03460050081025
32. Peters, S.A.E., Huxley, R.R. & Woodward, M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia **57**, 1542–1551 (2014). https://doi.org/10.1007/s00125-014-3260-6.
33. National Heart, Lung, and Blood Institute. Women and Heart Disease. Accessed November 10, 2022. https://www.nhlbi.nih.gov/health/coronary-heart-disease/women
34. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med. 1989 Sep 7;321(10):641-6. doi: 10.1056/NEJM198909073211004. PMID
35. The connection between menopause and cardiovascular disease risk...American Heart Association . https://www.heart.org › news › 2023/02/20 › the-conn 3; PMCID: PMC9066596
36. Anagnostis P, Lambrinoudaki I, Stevenson JC, Goulis DG. Menopause-associated risk of cardiovascular disease. Endocr Connect. 2022 Apr 22;11(4):e210537. doi: 10.1530/EC-21-0537. PMID: 3525848.

37. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol.* 2016;1(7):767–776. doi:10.1001/jamacardio.2016.2415

38. Abbey M, Owen A, Suzakawa M, Roach P, Nestel PJ. Effects of menopause and hormone replacement therapy on plasma lipids, lipoproteins and LDL-receptor activity. Maturitas. 1999 Dec 15;33(3):259-69. doi: 10.1016/s0378-5122(99)00054-7. PMID: 10656504

39. Wannamethee SG, Papacosta O, Lawlor DA et al (2012) Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia 55:80–87 doi: 10.1007/s00125-011-2284-4. Epub 2011 Aug 23. PMID: 21861177.

40. Howard BV, Cowan LD, Go O et al (1998) Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. Diabetes Care. 1998 Aug;21(8):1258-65. doi: 10.2337/diacare.21.8.1258. PMID: 9702430.

41. Ossei-Gerning N, Wilson IJ, Grant PJ (1998) Sex differences in coagulation and fibrinolysis in subjects with coronary artery disease. Thromb Haemost. 1998 Apr;79(4):736-40. PMID: 9569183.
42. White SJ, Newby AC, Johnson TW. Endothelial erosion of plaques as a substrate for coronary thrombosis. Thromb Haemost. 2016 Mar;115(3):509-19. doi: 10.1160/TH15-09-0765. Epub 2016 Jan 21. PMID: 26791872.
43. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, Mancini GBJ. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. J Am Coll Cardiol. 2017 Aug 29;70(9):1148-1158. doi: 10.1016/j.jacc.2017.06.053. PMID: 28838364.
44. Adlam D, Alfonso F, Maas A, Vrints C; Writing Committee. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD study group: a position paper on spontaneous coronary artery dissection.Eur Heart J**.** 2018; 39:3353–3368. doi: 10.1093/eurheartj/ehy080
45. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous Coronary Artery Dissection Associated With Pregnancy. J Am Coll Cardiol. 2017 Jul 25;70(4):426-435. doi: 10.1016/j.jacc.2017.05.055. PMID: 28728686.
46. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol. 2009 Oct 20;54(17):1561-75. doi: 10.1016/j.jacc.2009.04.098. PMID: 19833255; PMCID: PMC2789479.
47. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. JACC Cardiovasc Interv. 2015 Sep;8(11):1445-1453. doi: 10.1016/j.jcin.2015.06.017. PMID: 26404197.
48. Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, Reichek N, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. Am Heart J. 2001 May;141(5):735-41. doi: 10.1067/mhj.2001.114198. PMID: 11320360.

49. Bairey Merz CN, Pepine CJ, Shimokawa H, Berry C. Treatment of coronary microvascular dysfunction. Cardiovasc Res. 2020 Mar 1;116(4):856-870. doi: 10.1093/cvr/cvaa006. PMID: 32087007; PMCID: PMC7061279.
50. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007 Feb 22;356(8):830-40. doi: 10.1056/NEJMra061889. PMID: 17314342.
51. Gehrie ER, Reynolds HR, Chen AY, Neelon BH, Roe MT, Gibler WB, et al. Characterization and outcomes of women and men with non–ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J. 2009 Oct;158(4):688-94. doi: 10.1016/j.ahj.2009.08.004. PMID: 19781432.
52. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GJ, Feit F, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation. 2011 Sep 27;124(13):1414-25. doi: 10.1161/CIRCULATIONAHA.111.026542. Epub 2011 Sep 6. PMID: 21900087; PMCID: PMC3619391..
53. Robert Sykes, Daniel Doherty, Kenneth Mangion, Andrew Morrow, Colin Berry, What an Interventionalist Needs to Know About MI with Non-obstructive Coronary Arteries, Interventional Cardiology Review 2021;16:e10.https://doi.org/10.15420/icr.2021.10

54. Milner KA, Funk M, Richards S, Wilmes RM ,Vaccarino V, Krumholz HM. Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol. 1999;84:396- 399. doi: 10.1016/s0002-9149(99)00322-7. PMID: 10468075.

55. Ferry A.V., Anand A., Strachan F.E., Mooney L., Stewart S.D., Marshall L., Chapman A.R., Lee K.K., Jones S., Orme K., et al. Presenting Symptoms in Men and Women Diagnosed with Myocardial Infarction Using Sex-Specific Criteria. J. Am. Heart Assoc. 2019;8:e012307. doi: 10.1161/JAHA.119.012307.
56. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA, D'Onofrio G. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation. 2018 Feb 20;137(8):781-790. doi: 10.1161/CIRCULATIONAHA.117.031650. PMID: 29459463; PMCID: PMC5822747.
57. Khan NA, Daskalopoulou SS, Karp I, Eisenberg MJ, Pelletier R, Tsadok MA, Dasgupta K, Norris CM, Pilote L; GENESIS PRAXY Team. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med. 2013 Nov 11;173(20):1863-71. doi: 10.1001/jamainternmed.2013.10149. PMID: 24043208.
58. van Oosterhout REM, de Boer AR, Maas AHEM, Rutten FH, Bots ML, Peters SAE. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. J Am Heart Assoc. 2020 May 5;9(9):e014733. doi: 10.1161/JAHA.119.014733. Epub 2020 May 4. PMID: 32363989; PMCID: PMC7428564.
59. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. BMJ. 1994 Apr 2;308(6933):883-6. doi: 10.1136/bmj.308.6933.883. PMID: 8173366; PMCID: PMC2539855.
60. Pathak LA Pathak LA, Shirodkar S, Ruparelia R, Rajebahadur J. Coronary artery disease in women. Indian Heart J. 2017 Jul-Aug;69(4):532-538. doi: 10.1016/j.ihj.2017.05.023. Epub 2017 Jun 12. PMID: 28822527; PMCID: PMC5560902
61. Chiha J, Mitchell P, Gopinath B, Plant AJH, Kovoor P, Thiagalingam A. Gender differences in the severity and extent of coronary artery disease. Int J Cardiol Heart Vasc. 2015 Jul 30;8:161-166. doi: 10.1016/j.ijcha.2015.07.009. PMID: 28785696; PMCID: PMC5497284.
62. Kim HL, Kim HJ, Kim M, Park SM, Yoon HJ, Byun YS, Park SM, Shin MS, Hong KS, Kim MA. Sex differences in coronary angiographic findings in patients with stable chest pain: analysis of data from the KoRean wOmen'S chest pain rEgistry (KoROSE). Biol Sex Differ. 2022 Jan 3;13(1):2. doi: 10.1186/s13293-021-00411-1. PMID: 34980251; PMCID: PMC8722299
63. Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L; Get With the Guidelines Steering Committee and Investigators. Sex differences in medical care and early death after acute myocardial infarction. Circulation. 2008 Dec 16;118(25):2803-10. doi: 10.1161/CIRCULATIONAHA.108.789800. Epub 2008 Dec 8. PMID: 19064680.
64. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, Gebhard C. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. Eur Heart J. 2020 Apr 1;41(13):1328-1336. doi: 10.1093/eurheartj/ehz898. PMID: 31876924.
65. Lansky AJ, Hochman JS, Ward PA, Mintz GS, Fabunmi R, Berger PB, New G, Grines CL, Pietras CG, Kern MJ, Ferrell M, Leon MB, Mehran R, White C, Mieres JH, Moses JW, Stone GW, Jacobs AK; American College of Cardiology Foundation; American Heart Association. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. Circulation. 2005 Feb 22;111(7):940-53. doi: 10.1161/01.CIR.0000155337.50423.C9. Epub 2005 Feb 1. PMID: 15687113.
66. Alfredsson J, Stenestrand U, Wallentin L, Swahn E. Gender differences in management and outcome in non-ST-elevation acute coronary syndrome. Heart. 2007 Nov;93(11):1357-62. doi: 10.1136/hrt.2006.102012. Epub 2006 Nov 3. PMID: 17085528; PMCID: PMC2016903.
67. Doyle F, De La Harpe D, McGee H, Shelley E, Conroy R. Gender differences in the presentation and management of acute coronary syndromes: a national sample of 1365 admissions. Eur J Cardiovasc Prev Rehabil. 2005 Aug;12(4):376-9. doi: 10.1097/01.hjr.0000160725.82293.63. PMID: 16079646.
68. Khan E, Brieger D, Amerena J, Atherton JJ, Chew DP, Farshid A, Ilton M, Juergens CP, Kangaharan N, Rajaratnam R, Sweeny A, Walters DL, Chow CK. Differences in management and outcomes for men and women with ST-elevation myocardial infarction. Med J Aust. 2018 Aug 6;209(3):118-123. doi: 10.5694/mja17.01109. Epub 2018 Jul 23. PMID: 30025513.

69. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999 Jul 22;341(4):217-25. doi: 10.1056/NEJM199907223410401. PMID: 10413733.
70. Sharaf B, Wood T, Shaw L, Johnson BD, Kelsey S, Anderson RD, Pepine CJ, Bairey Merz CN. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. Am Heart J. 2013 Jul;166(1):134-41. doi: 10.1016/j.ahj.2013.04.002. Epub 2013 May 2. PMID: 23816032; PMCID: PMC370358