Vakhtangadze *et al. Vessel Plus* 2017;1:43-8
DOI: 10.20517/2574-1209.2016.05

Vessel Plus
www.vpjournal.net

Editorial **Open Access**

Myocardial ischemia in women: problems and challenges

Tamar Vakhtangadze[1], Nino Gakhokidze[2]

[1]*Research Institute of Clinical Medicine, Tbilisi Medical Academy, Caucasian International University, Tbilisi 0113, Georgia.*
[2]*AIETI Medical School, Dighomi, Tbilisi 0159, Georgia.*

Correspondence to: Prof. Tamar Vakhtangadze, Research Institute of Clinical Medicine, Tbilisi Medical Academy, Caucasian International University, Tevdore Mgvdeli street 13, Tbilisi 0113, Georgia. E-mail: tamarvakh@yahoo.com

How to cite this article: Vakhtangadze T, Gakhokidze N. Myocardial ischemia in women: problems and challenges. Vessel Plus 2017;1:43-8.

Article history: Received: 25-09-2016 Accepted: 26-12-2016 Published: 27-06-2017

Dr. Tamar Vakhtangadze is an Associate Professor of Tbilisi Medical Academy, Assistant Professor of Caucasus International University, Cardiologist at Research Institute of Clinical Medicine, Head of Cardiology Service at Medical Centre of GEOSWISS, Head of Outpatient Cardiology Service at St. Joakim and Anna Medical Centre. She is the Fellow of European Society Cardiology, member of the board of Georgian Society of Cardiology, Head of working group on women's cardiovascular morbidity of Georgian Society of Cardiology, member of the board of Georgian Society of Atherosclerosis, Executive Director of Georgian Society of Atherosclerosis, member of editorial board of journal "*Actual Topics of Women's Health*". She is author of more than 60 publications. Her main fields of interest include ischemic heart disease, atherosclerosis, heart failure, cardiomyopathies, women's cardiovascular health, and noninvasive imaging.

INTRODUCTION

Even in the 21st century, cardiovascular disease (CVD) remains an important public health issue because it is associated with high rates of mortality and morbidity.[1-5] In addition, the costs of treating and managing these patients are very high, as such patients have a constant need for medical treatment and their management often requires sophisticated and expensive tests.[6] The use of preventive measures, identification of high-risk groups,[7] early diagnosis, and treatment of women presenting with cardiovascular problems can all have a significant influence on reducing cardiovascular mortality, morbidity, and treatment costs, as has been shown in various countries.

For a long time, it was thought that CVD predominantly affects men. However, over the last two decades, it has been revealed women have higher rates of cardiovascuar morbidity and mortality. For example, 49% of European women die from CVD, compared with 41% of men.[3] At present, the basic statistical facts are as follows:[1,3,5,8]

• Worldwide, one-third of all deaths among women are due to CVD, with up to 8.6 million women dying from CVD each year. Furthermore, stroke kills more women than men (11% *vs*. 8.4%).

• More than two-thirds (approximately 42%) of women who have heart attacks die within 1 year, compared with 24% of men.

• Under the age of 50 years, women have double the risk of death after a heart attack than men.

• Heart attack and heart failure kill 6 times more women than breast cancer every year.

Quick Response Code:

By the end of the 1990s, cardiovascular morbidity in women started to drew particular attention, leading to studies and intensive work by the world's top cardiology societies. At the European Society of Cardiology 2005 conference, for example, very interesting data were presented about the situation in Europe.[9] It was revealed that:

- Women are underrepresented in cardiovascular research and trials.
- Women are less likely to analyze the influence of their risk factors on morbidity and mortality rates, and awareness about CVD among women is low.
- Women are less likely to undergo primary and secondary prevention.
- Women seek medical care less often than men.
- Fewer women than men undergo diagnostic tests, which results in a delay in diagnosis and a resulting delay in treatment.

Currently, the following categories of women's cardiovascular health are provided in modern guidelines:[10,11]

High risk (at least one high-risk state): clinical manifestations of coronary heart disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic kidney disease, diabetes, coronary heart disease with a 10-year risk > 10%.

At risk (at least one risk factor from the following): tobacco consumption, arterial hypertension (systolic pressure > 120 mmHg, diastolic pressure > 80 mmHg, or treatment with antihypertensive drugs), total cholesterol > 200 mg/dL, high-density lipoprotein cholesterol < 50 mg/dL or treatment of dyslipidemia, obesity (especially central obesity), poor nutrition, low physical activity, family history of premature CVD occurring in a first-degree relative in men aged < 55 years or women aged < 65 years, the metabolic syndrome, evidence of subclinical atherosclerosis, poor exercise capacity on treadmill test and/or abnormal heart rate recovery, systemic autoimmune collagen vascular disease (e.g. lupus, rheumatoid arthritis), history of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension.

Ideal cardiovascular health: total cholesterol < 200 mg/dL, arterial blood pressure < 120/80 mmHg, fasting glucose < 100 mg/dL, non-smoker, healthy diet.

Raising awareness of gender-specific risk factors will have an impact on women's cardiovascular health. The purpose of this article is to evaluate the modern views with respect to the diagnostic tools used to determine ischemia in women.

PATHOPHYSIOLOGICAL FEATURES OF MYOCARDIAL ISCHEMIA IN WOMEN

In general, the pathophysiological features of myocardial ischemia differ in women and men. There is a significant amount of data implicating the influence of sex hormones on the presentation of chest pain and electrocardiograph (ECG) changes.

In the mid-1990s, the US National Heart, Lung, and Blood Institute sponsored the Women's Ischemia Syndrome Evaluation (WISE) study, one of the cornerstones in the evaluation of myocardial ischemia in women,[12] which assessed 936 women with chest pain. The aims of the study were to optimize the evaluation of symptoms and diagnostic tests; to explore the mechanisms of symptoms and of myocardial ischemia in the absence of epicardial coronary artery stenosis; and to evaluate the influence of reproductive hormones on symptoms and the results of diagnostic tests.[12-14]

The results of the study were published in scientific papers over a long period of time. Based on these results, four groups of women with chest pain have been described:

1. Women with severe obstructive coronary artery disease (CAD) and myocardial ischemia.
2. Women with obstructive CAD but without myocardial ischemia.
3. Women without obstructive CAD but with myocardial ischemia.
4. Women without obstructive CAD and without myocardial ischemia.

One of the conclusions of the WISE study: quality of life is determined more by chest pain than by the presence of myocardial ischemia.

Women falling into the above categories present daily at medical facilities with chest pain, dyspnea, or other symptoms, and the proper differentiation of any underlying conditions will determine the need for further investigations and the most appropriate treatment options. These underlying conditions are macrovascular diseases, obstructive coronary atherosclerosis, and microvascular disease.

Among the women included in the WISE study, 37% did not have angiographic evidence of obstructive CAD; rather, they presented with normal or nearly normal coronary arteries (< 20% stenosis). In 25% of women, non-obstructive CAD was found (at least one 20-50% stenosis). And in 38% of patients included in the study, severe obstructive CAD was revealed (> 50% stenosis). Therefore, 62% of women with angina included in the study did not have severe obstructive CAD.[12-14]

Similar results have been obtained in other studies. In 2015, Lee *et al*.[15] published the results of a prospective study that evaluated patients with non-obstructive CAD. Overall, 77% of patients in the cohort were women; 44% of all patients had endothelial dysfunction, 21% had microvascular impairment, and 5% had a reduced fractional flow reserve. In 23% of cases, it was not possible to determine the cause of coronary symptoms. This study confirmed the results of previous studies[16-18] indicating that while the symptoms of CAD are well understood, women tend to develop symptoms 10-15 years later than men, and have more risk factors by the time of symptom onset. The study by Lee *et al*.[15] did not evaluate the influence of hormonal factors on the clinical presentation of symptoms.

Thus, an incomplete understanding of the sex-specific physiology of myocardial ischemia and underdeveloped diagnostic and treatment options may lead to the inadequate management of a large proportion of the population and a large number of women without signs of obstructive CAD at coronary angiography presenting with symptom-related disability. All of this consumes a considerable amount of healthcare resources.[6]

A European study published in 2012 found that angina in patients with normal blood vessels or non-obstructive atherosclerosis was associated with an increased risk of the combined endpoint of cardiovascular death, hospitalization due to myocardial infarction, heart failure, or stroke of up to 52% in the case of patients with normal coronary arteries and 85% in those with non-obstructive coronary atherosclerosis. In addition, these patients had an increased risk of all-cause mortality of up to 29% and 52%, respectively, with no differences between men and women.[19] Such physiological patterns have also been reported in other studies evaluating invasive and non-invasive coronary flow reserve.[20,21] All of these findings demonstrate the importance of evaluating and managing women with non-obstructive CAD.

Morphological studies have shown that the development of myocardial infarction is based on plaque rupture, plaque ulceration, and plaque calcification.[22] Plaque erosion/ulceration is another pathophysiological mechanism of myocardial infarction. In this case, damage of the integrity of the plaque cap leads to the development of a thrombus, with emboli from the plaque travelling to areas distal to the plaque and eventually blocking the lumen of the vessel. In most cases, this mechanism underlies the development of myocardial infarcts in women, and this type of non-obstructive atherosclerosis of coronary arteries is found more commonly in women with myocardial infarction than in men.[14,17,20-22]

The difference between men and women also exists in stable coronary syndromes. As noted above, in the WISE study, only 38% of women with a stable coronary syndrome had severe obstructive CAD, and the rest (62%) showed evidence of non-obstructive CAD.[13,14,17,20]

CORONARY MICROVASCULAR DYSFUNCTION

Myocardial ischemia is usually caused by narrowing of epicardial coronary arteries. Over the past 30 years, however, many studies have revealed that impaired coronary microcirculation can also lead or contribute to the development of ischemia of myocardial cells.

Most of the articles published on myocardial ischemia have been designed to evaluate coronary obstruction and to determine strategies for the early detection of obstructive CAD. However, there is lack of research on detection of ischemia in patients with normal or non-obstructive coronary arteries, which mainly present in women. As previously mentioned, women are less likely than men to undergo diagnostic or preventive measures. Since the 1980s, the information about microvascular disease has expanded. In 2007, Camici and Crea[23] evaluated clinical settings in which myocardial ischemia occurs and proposed a classification of coronary microvascular dysfunction (CMVD) based on the underlying diseases in which it occurs (e.g. obstructive CAD, cardiomyopathy, and systemic diseases). Their classification is as follows:

- Class 1: CMVD in the absence of obstructive CAD and myocardial diseases.
- Class 2: CMVD in the presence of myocardial diseases.
- Class 3: CMVD in the presence of obstructive CAD.
- Class 4: CMVD caused by coronary recanalization (i.e. iatrogenic).

In an everyday setting, it is very difficult to distinguish the forms of CMVD because small coronary arteries cannot be visualized by angiography. During invasive investigations, complex, time-consuming, and costly methods are required to carefully assess the function of the coronary microcirculation. In patients suspected of having microvascular angina, accepted hallmarks of myocardial ischemia, such as stress-induced left ventricular contractile alterations,[23-26] are usually undetectable. A sparse distribution of myocardial ischemia in a patient presenting with CMVD is, on one hand, sufficient to produce ECG changes and myocardial perfusion defects on single-photon emission computed tomography (SPECT); but, on the other hand, might not result in detectable contractile abnormalities because of normal function of the surrounding myocardial tissue.[26,27]

EVALUATION AND DIAGNOSIS

The high incidence of cardiovascular death in women, particularly due to CAD, raises the need for the early evaluation of women at increased risk in order to determine the optimal therapeutic strategies. Coronary angiography remains the reference standard for diagnosing ischemic heart disease. However, it has very low possibilities to evaluating patients with microvascular angina. Because the majority of patients with microvascular dysfunction are women, it is very important to determine which tests are of value for their evaluation. Coronary angiography cannot provide information about the severity and extent of ischemia. Thus, in women, non-invasive tests that save money and reduce periprocedural risks, are of particular value.

The simplest formula - ischemia is mismatch between oxygen demand and delivery - indicates the importance of the direct visualization of ischemia in women, particularly because the rate of microvascular angina is higher in women than in men. Exercise stress testing remains the basis for the evaluation and risk-stratification of patients with suspected CAD. It is a valuable and informative tool in both men and women. However, the accuracy of interpreting the test depends not only on ST-segment changes, but also on the double product, heart-rate recovery time, and so on. To accurately interpret the results of the test, the pretest probability of the patient having ischemic heart disease and her hormonal state should be considered. It is well known that during the physical exercise test (treadmill or veloergometer), increased oxygen demand and energy consumption lead to ECG changes.[28-32]

It is also well known that an exercise stress test has relatively lower sensitivity and specificity for diagnosing ischemia. Meta-analyses have indicated that there are frequent false-positive and false-negative results, and that this test is more valuable in young patients compared with older ones.[29,30] This view has been echoed in other meta-analysis.[32,33] An analysis of ECG results acquired during exercise stress tests found sensitivity and specificity of 64% and 81%, respectively, in men, compared with 61% and 65%, respectively, in women -- quite a big difference in specificity between men and women. Analyses for other imaging modalities have found sensitivities and specificities, respectively, of: 77% and 81% for men compared with 78% and 86% for women for stress echocardiography; 88% and 74% for men compared with 82% and 81% for women for SPECT; and 86% and 82% for men compared with 78% and 74% for women for magnetic resonance imaging (MRI).[33] In all of these studies, the standard for diagnosis (and comparison) was coronary angiography and the presence of obstructive CAD.

But how about the detection of microvascular disease? Angiography cannot record it. Is there a standard for diagnosing microvascular disease? To answer these questions, the physiology of tests should be considered. The major advantage of the exercise ECG is that it is inexpensive, and therefore readily and widely available. However, quantification of the extent of microvascular dysfunction is not possible.

Direct visualization of the blood supply and hence ischemia is possible only by studying perfusion via the well-established tool SPECT and the emerging tool MRI.

The advantages of SPECT stress perfusion images include direct visualization of ischemia, high interobserver agreement, low operator dependence, a high technical success rate, high sensitivity, better accuracy when multiple resting left ventricular motion abnormalities are present, and the ability to detect ischemia in an infarct area. Higher specificity, and greater availability, versatility, and (arguably) convenience favor the use of stress echocardiography over SPECT.[33-35] However, the lower specificity of SPECT compared to stress-echocardiography may correspond to the presence of microvascular disease, which does not currently have clear diagnostic criteria. Data regarding the use of MRI in this context remain limited and insufficient. However, it is seems promising.

Quantitative rest/stress myocardial perfusion imaging [best documented using positron emission tomography (PET)] combined with clinical circumstances usually provides a definitive direct visualization of ischemia, and is therefore a highly informative tool in the diagnosis of patients and guiding management, including risk-factor management and revascularization for patients with physiologically severe epicardial stenosis by quantitative PET.[36]

Compared with negative tests, a positive result on computed tomography angiography (CTA) in women has been found to be more predictive of subsequent clinical events than a positive stress test (adjusted P = 0.028).[32] Among men, a positive CTA was slightly but not significantly less informative of risk detection than a positive stress test (adjusted P = 0.168).[28,37,38]

However, all of these results, and all of the sensitivity and specificity data, refer to the evaluation of patients with obstructive CAD. There are very few data on the value of these tests in diagnosing microvascular angina, and this represents a main limitation of current research.

Evaluating women with chest pain seems to be difficult, with various pathophysiologic mechanisms behind the condition, diverse clinical presentations, and limited

diagnostic standards. Hence there is no single test that will definitely diagnose ischemia due to microvascular disease in women.[39] Even after a normal exercise-stress test, further testing may be needed to gain important diagnostic information. Further research is aimed for optimizing the non-invasive identification and management of CMVD in such patients.

Authors' contributions

Study design: T. Vakhtangadze
Data collection: N. Gakhokidze
Manuscript writing: T. Vakhtangadze, N. Gakhokidze
Manuscript review: T. Vakhtangadze

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

REFERENCES

1. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;133:e38-360.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistic--2015 update: a report from the American Heart Association. *Circulation* 2015;131:e29-322.
3. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016;37:3232-45.
4. Center for Disease Control and Prevention. Women and heart disease fact sheet. Available from: http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm. [Last Accessed on 2017 Jan 11].
5. American Heat Association; American Stroke Association. Heart disease and stroke statistics - at-a-glance. Available from: https://www.heart.org/idc/groups/ahamah-public/@wcm/@sop/@smd/documents/downloadable/ucm_470704.pdf. [Last Accessed on 2017 Jan 11].
6. Vieira RD, Hueb W, Hlatky M, Favarato D, Rezende PC, Garzillo CL, Lima EG, Soares PR, Hueb AC, Pereira AC, Ramires JA, Kalil Filho R. Cost-effectiveness analysis for surgical, angioplasty, or medical therapeutics for coronary artery disease: 5-year follow-up of medicine, angioplasty, or surgery study (MASS) II trial. *Circulation* 2012;126:S145-50.
7. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;123:933-44.
8. Women's Heart Foundation. Women and heart disease facts. Available from: http://www.womensheart.org/content/HeartDisease/heart_disease_facts.asp. [Last Accessed on 2017 Jan 17].
9. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, Jonsson B, Schenck-Gustafsson K, Tendera M. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006;27:994-1005.
10. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701.
11. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation* 2011;123:1243-62.
12. Merz CN, Kelsey SF, Pepine CJ, Reichek N, Reis SE, Rogers WJ, Sharaf BL, Sopko G. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. *J Am Coll Cardiol* 1999;33:1453-61.
13. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol* 2012;35:141-8.
14. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009;169:843-50.

15. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015;131:1054-60.
16. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;33:734-44.
17. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN; ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol* 2015;66:1918-33.
18. Bairey Merz N, Bonow RO, Sopko G, Balaban RS, Cannon RO 3rd, Gordon D, Hand MM, Hayes SN, Lewis JF, Long T, Manolio TA, Maseri A, Nabel EG, Desvigne Nickens P, Pepine CJ, Redberg RF, Rossouw JE, Selker HP, Shaw LJ, Waters DD; National Heart, Lung and Blood Institute; American College of Cardiology Foundation. Women's Ischemic Syndrome Evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: executive summary. *Circulation* 2004;109:805-7.
19. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;33:734-44.
20. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G, Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol* 2010;55:2825-32.
21. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, Di Carli MF. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129:2518-27.
22. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation* 2016;133:916-47.
23. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007;356:830-40.
24. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. *J Am Coll Cardiol* 1991;18:1463-70.
25. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilsizian V, Cannon RO 3rd. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;29:293-301.
26. Pargaonkar V, Khandelwal A, Kobayashi Y, Tanaka S, Mathur MB, Froelicher V, Yeung A, Tremmel J. The diagnostic value of stress echocardiography and electrocardiography in identifying occult coronary abnormalities in patients with angina and no obstructive coronary artery disease. *J Am Coll Cardiol* 2015;65:A1623.
27. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010;121:2317-25.
28. Visser F. Non invasive assessment of coronary microvascular dysfunction. *Heart Metab* 2008;40:15-19.
29. Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. *Int J Clin Pract* 2012;66:477-92.
30. Shah SF, Meo SA. Usefulness of standard treadmill stress testing in women. *J Pak Med Assoc* 2009;59:197-200.
31. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. *Circulation* 2010;122:2570-80.
32. Sanders GD, Patel MR, Chatterjee R, Ross AK, Bastian LA, Coeytaux RR, Heidenfelder BL, Musty MD, Dolor RJ. Noninvasive technologies for the diagnosis of coronary artery disease in women: future research needs. Future research needs paper no. 41. (Prepared by the Duke Evidence-based Practice Center under contract No. 290-2007-10066-I). AHRQ Publication No. 13-EHC072-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2013. Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm. [Last Accessed on 2017 Jan 17].
33. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol* 1999;83;660-6.
34. Galiuto L, Picano E. Stress echo in microvascular disease. In: Picano E. Stress echocardiography. 6th ed. Berlin: Springer International Publishing; 2015. p. 485-507.
35. Marwick TH, Picano E, Marraccini P, Schwitter J, Senior R. Comparison with other imaging techniques. In: Picano E. Stress echocardiography. 6th ed. Berlin: Springer International Publishing; 2015. p. 627-59.
36. Cavusoglu Y, Entok E, Timuralp B, Vardareli E, Kudaiberdieva G, Birdane A, Gorenek B, Unalir A, Goktekin O, Ata N. Regional distribution and extent of perfusion abnormalities, and the lung to heart uptake ratios during exercise thallium-201 SPECT imaging in patients with cardiac syndrome X. *Can J Cardiol* 2005;21:57-62.
37. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging microvascular dysfunction and mechanisms for female-male differences in CAD. *JACC Cardiovasc Imaging* 2016;9:465-82.
38. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, Gill EB, Johnson BD, Kenkre T, Handberg EM, Li D, Sharif B, Berman DS, Petersen JW, Pepine CJ, Bairey Merz CN. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. *Circ Cardiovasc Imaging* 2015;8:e002481.
39. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;372:1291-300.