Published in final edited form as:

Can J Cardiol. 2014 July ; 30(7): 747–755. doi:10.1016/j.cjca.2013.08.013.

Sex-Specific Factors in Microvascular Angina

Tara Sedlak, MD^{#1,3}, Mona Izadnegahdar, PhD^{#3}, Karin H. Humphries, DSc^{2,3}, and C. Noel Bairey Merz, MD⁴

¹Vancouver General Hospital, Vancouver, British Columbia, Canada

²Providence Health Care Research Institute, St. Paul's Hospital, Vancouver, British Columbia, Canada

³Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada

⁴Barbra Streisand Women's Heart Center, Cedars-Sinai Heart Institute, Los Angeles, CA

These authors contributed equally to this work.

Abstract

Among women presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common, as compared to men. These women are often labeled as cardiac syndrome X (CSX), a subset of which have microvascular angina (MA) due to microvascular coronary dysfunction (MCD). MCD is not benign and is associated with an annual 2.5% cardiac event rate. Non-invasive testing for MCD remains insensitive although newer imaging modalities such as adenosine cardiac magnetic resonance imaging (CMRI) appear promising. The gold standard for diagnosis of MCD is coronary reactivity testing (CRT), an invasive technique which is not available in many countries. With regard to treatment, large scale trials are lacking. While research is ongoing, the current platform of therapy consists of anti-anginal, anti-platelet and endothelial modifying agents (primarily angiotensin converting enzyme inhibitors and statins).

Introduction

Among women presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common, as compared to men.¹ Other studies demonstrate that women are less likely than age-matched men to have obstructive coronary artery disease (CAD).² These women are often labeled as cardiac syndrome X (CSX), defined as the triad of chest pain, abnormal stress testing consistent with ischemia and absence of obstructive CAD (i.e. 50% stenosis in 1 coronary artery) on coronary angiography.³

© 2013 Canadian Cardiovascular Society. Published by Elsevier Inc. All rights reserved.

Address for correspondence: C. Noel Bairey Merz, MD, 127 S. San Vicente Blvd., A3600, Los Angeles, California 90048, Phone: (310) 423-9680, Fax: (310) 423-9681, merz@cshs.org..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CSX is classically acknowledged as a female predominant disorder and nearly 70% of patients diagnosed as having CSX are women.⁴ Among subjects suspected to have myocardial ischemia and referred for clinically indicated coronary angiography, 41% of women versus only 8% of the men studied showed non-significant epicardial CAD.¹ The large Coronary Artery Surgery Study (CASS) of nearly 25,000 subjects evaluated after undergoing angiography, further points towards the female predominance of having chest pain with normal coronary arteries.⁵ More recently, similar results have been described with coronary computed tomographic angiography (CCTA).⁶

Symptom-driven care for women in the absence of obstructive CAD is substantial.⁷ For women with signs and symptoms of ischemia but no obstructive CAD the average lifetime cost for ischemic heart disease (IHD) is \$ 767,288, comparable to the magnitude of more than \$1 million dollars for women with obstructive CAD. Based on these data, we have estimated the societal economic burden for CAD care for women with angina could exceed \$162 billion dollars annually in the US, with approximately half of this expenditure on women with no obstructive CAD.⁷ While some studies on ongoing in this area, there is a clear need for future research on microvascular angina and some suggestions for future research ideas are presented in Table 1.

Pathogenesis

A subset of patients with CSX have microvascular angina (MA)⁸ due to microvascular coronary dysfunction (MCD). The conditions of CSX and its subentity MA due to MCD, are increasingly investigated yet full elucidation of their pathogenesis remains lacking. Despite the considerable effort of research over the last 4 decades⁹, there is no universally accepted understanding of the pathogenesis of signs and symptoms of ischemia and no obstructive CAD.^{9,10} Suggested mechanisms⁹⁻¹¹ of CSX include altered regulation of coronary microcirculation through autonomic dysregulatory and endothelial mechanisms, generalized vascular disorder and abnormal subendocardial perfusion. Other suggested contributing factors include inflammation, hyperinsulinemia, enhanced sodium-hydrogen exchange, hormonal deficiency, abnormal pain perception and lastly inherent pathogenetic pathways.

MA due to MCD appears to be a major etiologic mechanism underlying chest pain evoked by ischemia in patients with CSX (Figure 1). It refers to abnormalities in the vasomotor or metabolic regulators of the smaller resistance coronary arterioles (<500µm), although structural abnormalities of the microcirculation (for example smooth muscle cell hypertrophy) have been described by some¹², but not all studies.¹³ Although small coronary arterioles are not visualized during coronary angiography, they are the major determinants of coronary vascular resistance.¹⁴ Experimental studies and clinical observations emphasize the role of sex differences in microvascular pathophysiology.¹⁵ Evidence from autopsy data suggests that women may have a higher frequency of coronary plaque erosion and microembolization¹⁶, which could result in greater MCD. Results from retinal photography implicate sex-specific dysfunction of the microvasculature. Retinal arterial narrowing, a measure of microvascular disease, is related to cardiovascular disease risk and mortality in women but *not* in men.¹⁷

Diagnosis

Non-invasive Testing

Non-invasive testing for MCD remains insensitive although newer imaging modalities such as adenosine cardiac magnetic resonance imaging (CMRI) appear promising as more sensitive for detection of the ischemic cascade (Figure 2).

Exercise treadmill testing (ETT)—ST depression on standard ETT was the cornerstone to CSX diagnosis in the past. True microvascular pathology such as that seen in MCD, is not always captured on ETT however. In 1992, Camici *et al.* examined the correlation between the ECG during exercise stress and coronary vasodilator reserve by ¹³N-labeled ammonia and positron emission tomography in 45 patients with chest pain and normal coronary arteries.¹⁸ They reported good sensitivity (86%) in identifying patients with a blunted coronary flow reserve but poor specificity (45%).

Traditional stress imaging—Traditional cardiovascular imaging techniques are limited in their ability to image vessels <500µm in diameter. Therefore, stress imaging techniques such as stress echocardiography and nuclear perfusion stress testing remain insensitive in diagnosing MCD. Kaski *et al.* studied 99 patients with angina and normal coronary arteries.⁴ While transient ST depression on ETT was observed in 65% of patients, only 22% had abnormalities on nuclear myocardial perfusion imaging. Further, Nihoyannopoulos *et al.* studied stress echo in a similar population and reported that all patients with ST depression on ETT had a normal stress echo.¹⁹

Cardiac Magnetic Resonance Imaging (CMRI)—CMRI offers several advantages over traditional imaging techniques in the diagnosis of MCD. CMRI allows evaluation of subendocardial perfusion, fibrosis and microinfarction, assessment of left ventricular function and mass and measurement of myocardial flow reserve using a myocardial perfusion reserve index (MPRI). Lanza *et al.* compared CMRI and invasive coronary reactivity testing with adenosine in 18 CSX patients and 10 healthy controls.²⁰ Reversible perfusion defects on CMRI were found in 56% of CSX patients and 0% of controls. Further, CSX patients with CMRI perfusion defects had a lower CFR by invasive testing than those without perfusion defects. A large-scale NHLBI funded trial comparing CMRI and CRT with regard to sensitivity and specificity is ongoing and will provide future insights into this promising modality.

Invasive Testing

Coronary reactivity testing (CRT)—CRT is the gold standard technique for the diagnosis of MCD. Intra-coronary infusion of adenosine, acetylcholine and nitroglycerin allows assessment of microvascular and macrovascular endothelial and nonendothelial pathways and provides therapeutic targets for patients with MCD. The normal response to intra-coronary infusion of adenosine is a 2.5 increase in coronary flow reserve (CFR). Therefore, a CFR of <2.5 defines MCD and examines the non-endothelial dependent microvascular pathway. Acetylcholine uniformly dilates both the microvasculature and macrovasculature in an endothelial-dependent fashion. The normal response to acetylcholine

is an increase in coronary blood flow (CBF) of >50% above baseline and endothelial dysfunction may be manifest by a significant attenuation, no change or even a decrease in CBF. Finally, nitroglycerin tests the non-endothelial macrovascular pathway and lack of a response to nitroglycerin may indicate smooth muscle dysfunction. A recommended diagnostic and management approach for MCD including when to refer for coronary reactivity testing provided in Figure 3.

Intravascular ultrasound—While MCD patients by definition will have minimal CAD on standard coronary angiography, several studies have demonstrated significant atherosclerosis by intravascular ultrasound (IVUS).^{21,22} Khuddus *et al.* examined IVUS in 100 women with non-obstructive CAD (<50% stenosis in any epicardial artery). While 70% had no CAD on angiography, 79% had atherosclerosis on IVUS.²¹ This highlights one of the limitations of standard angiography in defining plaque burden in women.

Prognosis

Since the early 1970s, several studies have examined the prognosis of patients with angina symptoms suggestive of ischemia but without any evidence of obstructive CAD based on coronary angiography. The findings of these studies have been inconsistent, and to a large extent, not directly comparable due to a number of factors including, the differences in their patient populations under study (e.g. only including patients with no CAD or “normal” coronaries vs. including patients with nonobstructive CAD—mainly defined as <50% stenosis in any epicardial coronary artery), exclusion criteria (e.g. exclusion of patients with prior cardiovascular disease), follow-up time, or the differences in their outcome of interest (i.e. definition of major adverse cardiac event).

One of the earliest studies on the long-term outcome of CSX patients was based on the CASS registry, which included 4,051 patients with normal or near normal (<50% stenosis) coronary arteries. Based on this study, Kemp *et al.* found that the prognosis of these patients was favorable with a 7-year survival rate of 96% and 92%, respectively.²³ Similarly, other earlier studies focusing only on patients with angiographically normal coronary arteries, have also reported good long-term prognosis with low rates of mortality and morbidity.^{24,25} A meta-analysis comprised of 16 such studies, mainly with small sample sizes, has estimated a pooled rate of 1.5% per 5 years for major adverse cardiac events (death, myocardial infarction and revascularization).²⁶

However, more recent and larger studies have shown that the prognosis of patients with angina symptoms but without evidence of obstructive CAD is not as benign as it was once thought to be. Gulati *et al.* identified 540 women with stable angina but normal or nonobstructive CAD (< 50% stenosis), based on the Women’s Ischemia Syndrome Evaluation (WISE) study cohort, and compared their adverse cardiac outcomes to 1000 age- and race-matched asymptomatic women without any previous evidence of CAD.²⁷ The findings indicated that the 5-year rate of major adverse cardiovascular events (MACE) outcomes (i.e. hospitalization for myocardial infarction, heart failure, stroke, or cardiovascular death) were 3 fold higher in symptomatic women with normal coronary arteries and approximately 8 fold higher in symptomatic women with nonobstructive CAD,

as compared to asymptomatic women without CAD (7.9% and 16.0% vs. 2.4%, respectively). This difference remained statistically significant even after adjusting for the baseline differences in patient's risk profile. Of note, an age-stratified sub analysis of the findings, indicated that the difference in risk of MACE between women with normal coronaries and asymptomatic women without CAD, was only significant among younger patients, not among patients >62 years of age.

Furthermore, a Danish study by Jespersen *et al.* evaluated MACE outcomes (i.e. hospitalization for myocardial infarction, heart failure, stroke, or cardiovascular death) of 11,223 men and women with stable angina, as the indication for undergoing their first angiography, but with no evidence of obstructive CAD (< 50% stenosis).²⁸ The authors found that, regardless of sex, symptomatic patients with normal or nonobstructive CAD had elevated risk of MACE, as compared to a reference asymptomatic population selected from the Copenhagen City Heart study, with a pooled hazard ratio of 1.52 (95% CI: 1.27, 1.83) and 1.85 (95% CI: 1.51, 2.28), respectively. Similar to the findings of the study by Gulati *et al.*, the increase in risk of MACE in symptomatic patients without obstructive CAD was driven primarily by re-hospitalization for heart failure.

Sex Differences in Adverse Outcomes

The current understanding of sex differences in outcomes of patients with angina and no evidence of obstructive CAD is limited. Although, the findings of the WISE study have greatly contributed to a better understanding of the pathophysiology as well as the risk and predictors of adverse outcomes of these patients, the WISE study population was comprised of women only. Subsequently, a few studies have extended the findings of the WISE study by highlighting important sex differences in this area of research.

A study by Humphries *et al.*, in a large population-based setting, assessed the outcomes (re-hospitalization for ACS or chest pain) of 3,647 patients who underwent coronary angiography with an indication of stable angina or acute coronary syndrome but had angiographically normal coronaries.²⁹ The patients were identified using the BC Cardiac Registry, which collects information on all coronary angiography procedures performed in British Columbia, Canada. The authors found that, despite the overall favorable prognosis within the first year following initial angiography (1.0% died, 0.6% had stroke and 0.1% underwent revascularization), women were 4 times more likely to be re-hospitalized with a diagnosis of ACS or chest pain requiring angiography within the first 6 months. This difference remained significant even after adjusting for age and cardiac risk factors. Based on the same data source, Sedlak *et al.* evaluated the outcomes of 4,184 women and 9,511 men with chest pain and normal or nonobstructive coronary disease (<50% stenosis). Unlike the study by Humphries *et al.*, this study was based on patients with stable angina as the indication for undergoing coronary angiography. Although the findings indicated that patients with normal coronaries had low 1- and 3-year MACE rates, Sedlak *et al.* found that the prognosis of those with nonobstructive CAD, particularly women, was not benign. As compared to patients with no CAD, women with nonobstructive CAD had a 3.5 times greater hazard of MACE (i.e. hospitalization for myocardial infarction, heart failure, stroke, or all-cause mortality) within the first year post angiography (HR=3.58; 95%CI: 1.87, 6.86)

(Figure 4)³⁰. In contrast, the hazard of MACE in men with nonobstructive CAD was similar to men with no CAD (HR=0.82; 95%CI: 0.35, 1.93). With respect to sex differences in MACE outcomes, no difference was observed among patients with normal coronaries; in contrast, among patients with nonobstructive CAD, women had significantly higher risk of MACE as compared to men (HR=2.93; 95%CI: 1.30, 6.62).

However, a recent study by Johnston *et al.*, based on the Swedish Coronary Angiography and Angioplasty Register (SCARR), did not find any significant sex differences in adverse outcomes (i.e. any hospitalization for MI, any ischemic event, repeat coronary angiography and all-cause death) among stable angina patients with nonobstructive CAD.³¹ This inconsistency with prior findings may be explained by the differences in study outcomes. Specifically, this study did not include hospital readmission due to heart failure in their composite adverse outcome, while prior studies have indicated that the increased risk of MACE in patients with normal or non-obstructive CAD, particularly among women, is mainly driven by heart failure.

‘At-risk’ Populations with Elevated Risk of Adverse Outcomes

Among patients with chest pain but with nonobstructive CAD, in addition to female sex as independent predictor of elevated risk of adverse cardiac outcomes, emerging research suggests other contributing factors and ‘at-risk’ patient populations. These include patients with persistent chest pain and evidence for endothelial dysfunction. Based on the WISE study, Johnson *et al.* have shown that the 6-year incidence of MACE (readmission for MI, HF, stroke, and cardiac death) was twice as high in women with persistent chest pain (defined as chest pain symptoms still present at 1-year follow-up), as compared to women without persistent chest pain.³² Furthermore, several studies have shown that endothelial dysfunction in a setting of nonobstructive disease predicts the development of CAD in the long term and is associated with adverse cardiac outcomes.^{33,34}

Therapy

While a number of non-pharmacologic and pharmacological therapies have been tested in CSX and MA due to MCD subjects on the outcomes of angina, exercise performance and coronary blood flow (Table 2), no study has evaluated the impact on major adverse cardiac outcomes.

Non-pharmacologic Therapies

Most lifestyle changes are beneficial in women for primary prevention of cardiovascular disease (CVD) and secondary prevention of ischemic heart disease. Specifically, the INTERHEART study, a global case-control study involving 52 countries, demonstrated that regular physical activity was strongly protective of a future acute myocardial infarction in women.³⁵ Data from the Nurses Health Study (NHS) demonstrated that women who adhered to a healthy diet, were nonsmoking, engaged in moderate-to-vigorous exercise >30 min/day, maintained a BMI <25 and had moderate alcohol consumption, their risk for future CVD events compared to non-adherent women was reduced by 83%, RR 0.17 (95% CI, 0.07 to 0.41).³⁶ In the MCD population, Eriksson *et al.* demonstrated that regular aerobic

exercise (30 min, 3 times/week) decreased angina frequency and severity and improved endothelium-dependent blood flow in the brachial artery at 8 weeks however the number of patients studied was small and the level of significance was borderline ($p=0.05$).³⁷

With regard to other non-pharmacologic techniques, a recent study showed that an 8 week program of cognitive behavioral therapy (CBT) of autogenic training improved symptom frequency and severity in women with ischemia and non-obstructive coronary artery disease compared with controls ($p<0.001$).³⁸ Further, neurostimulation in the form of spinal cord stimulation has been shown to increase coronary blood flow, reduce duration and frequency of anginal attacks and reverse ST segment depression during stress testing compared to controls ($p<0.001$).³⁹ Patients with MCD and persistent angina have also been shown to benefit from Enhanced External Counterpulsation (EECP) therapy through reductions in angina and improvements in ischemia on traditional stress testing.⁴⁰ Specifically, in one study, at 12 months, 87% of patients had seen an improvement in angina by at least one Canadian Cardiovascular Society (CCS) class.

Pharmacologic Therapies

Anti-platelet agents—The 2011 effectiveness-based guidelines for the prevention of cardiovascular disease in women suggest a likely benefit from low dose aspirin in women >65 years particularly for stroke prevention.⁴¹ Since MCD patients are at elevated risk for future cardiovascular events compared to age and sex-matched controls, these guidelines can be extrapolated to recommend low dose aspirin in this group. Further, while coronary angiography often shows no significant CAD, IVUS has demonstrated significant coronary atherosclerosis in many MCD patients.²¹ Therefore, the CCS Guidelines for the use of antiplatelet therapy in the outpatient setting may be extrapolated to the use of low dose aspirin in MCD patients even in the <65 year old age category.⁴²

Statins—Most MCD patients will have plaque by IVUS and endothelial dysfunction on invasive CRT.²¹ Kayikcioglu *et al.* compared pravastatin 40 mg to placebo in 40 CSX women with an LDL <4.0 mmol/L and reported significant improvements in both brachial artery flow mediated dilation (FMD), a marker for endothelial dysfunction, and in exercise-induced ischemia.⁴³ Further Pizzi *et al.* reported improved FMD and quality of life following 6 months of atorvastatin 40 mg (in addition to an angiotensin converting enzyme inhibitor) when compared to placebo.⁴⁴ In MCD patients, it is therefore reasonable to prescribe statins with a goal LDL of <2.0 in those who qualify by the presence of risk factors, evidence of atherosclerosis, and/or endothelial dysfunction.

Anti-ischemic Agents—Nitrates, beta-blockers, and calcium channel blockers are commonly used in MCD patients with ongoing angina. An observational study of 99 patients with CSX showed that nitrates were effective anti-anginal therapy in 40-50% of the patients.⁴ Nitrate tolerance is common however and it is important to advise the patient to take nitrate-free intervals to prevent escalating doses. Beta-blockers improve chest pain frequency and severity in MCD patients when compared to nitrates and/or calcium channel blockers.⁴⁵ While research is yet to be done, the newer generations of beta-blockers with alpha-blocking properties (carvedilol) and anti-oxidant properties (nebivolol) may offer

additional benefits in the treatment of MCD in women. In women with coronary vasospasm, calcium channel blockers are first line therapy. In MCD patients however, diltiazem failed to improve CFR⁴⁶ and a meta-analysis by Heindenreich *et al.* found more patients on CCBs discontinued their medication due to side effects than those on beta-blockers ($p<0.001$).⁴⁷ Therefore, it is reasonable to conclude that beta-blockers should be used as first line therapy for anginal symptoms in MCD patients, reserving calcium channel blockers and nitrates for refractory cases and/or coronary vasospasm.

Angiotensin Converting Enzyme Inhibitors (ACEI)—Mechanistically, ACEI improve endothelial dysfunction through increasing endothelial nitric oxide bioavailability and reducing oxidative stress.^{44,48,49} In MCD patients, the WISE compared quinapril 80 mg daily to placebo and reported improvements in both CFR by invasive coronary reactivity testing ($p<0.019$) and angina frequency ($p=0.037$) with ACEI over 16 weeks.⁵⁰ Therefore, ACEI are recommended in women with MCD particularly in patients with a reduced ejection fraction, uncontrolled risk factors, and/or endothelial dysfunction demonstrated on invasive testing.

Phosphodiesterase-5 Inhibition—Sildenafil, a phosphodiesterase-5 inhibitor, was examined in 23 women with MCD and a baseline CFR of <3.0 on invasive CRT.⁵¹ Ingestion of 100mg of oral sildenafil resulted in acute improvement in CFR, particularly in those women with a baseline CFR of <2.5 suggesting possible use of this medication in patients who have not responded to traditional medications. As phosphodiesterase-5 inhibitors interact with nitrates and can produce significant hypotension, specific counseling must be given around minimizing nitrate use while on these agents.

Low Dose Tricyclic Medication—Low dose tricyclic anti-depressants (TCAs) such as imipramine and amitriptyline have been shown to increase exercise tolerance and decrease chest pain in CSX patients.⁵² They are particularly useful in patients with cardiac nociceptive abnormality and uncontrolled chest pain despite traditional use of anti-anginals.

L-arginine—L-arginine is a precursor of nitric oxide, which mediates vascular smooth muscle cell relaxation and inhibits platelet aggregation. In patients with non-obstructive CAD and ongoing chest pain, 3g TID of L-arginine improved both symptoms and CBF response to acetylcholine over placebo.⁵³ Caution must be used in post-MI patients however as the Vascular Interaction With Age in Myocardial Infarction (VINTAGE-MI) trial demonstrated an increase in mortality with L-arginine supplementation.⁵⁴

Other agents not available in Canada and the US—Ranolazine is a relatively new anti-anginal agent that is available in the USA, but not in Canada. It alters late sodium current and reduces calcium overload in the myocyte.⁵⁵ A small trial in women with MCD demonstrated angina improvement measured by the Seattle Angina Questionnaire on ranolazine compared to placebo as well as trends towards improvement in myocardial perfusion abnormalities by cardiac magnetic resonance imaging.⁵⁶ Larger studies are currently ongoing. Nicorandil is a drug available only in Europe and has two mechanisms of action: venodilation and arterial dilation. In small studies, it improved angina symptoms in CSX patients.⁵⁷ Ivabradine, also available only in Europe, inhibits the I_f (so called “funny”

channel) which is highly expressed in the sinoatrial node and therefore lowers heart rate. It has been shown to increase exercise duration in men and women with ischemic heart disease⁵⁸ but has not been examined specifically in the MCD population.

Conclusion

CSX and MA due to MCD are challenging medical conditions that predominantly impact women. New data improve our understanding of coronary vascular dysfunction and resultant myocardial ischemia that identifies the subgroup of MA due to MCD among patients with CSX. MCD has an adverse prognosis and health care cost expenditure comparable to obstructive CAD. The high prevalence of this condition, particularly in women, adverse prognosis and substantial health care costs, coupled with a lack of evidence regarding treatment strategies on prognosis, makes MA due to MCD an important research priority.

Acknowledgments

This work was supported by contracts from the National Heart, Lung and Blood Institutes, nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, a GCRC grant MO1-RR00425 from the National Center for Research Resources, and grants from the Gustavus and Louis Pfeiffer Research Foundation, Denville, New Jersey, the Women's Guild of Cedars-Sinai Medical Center, Los Angeles, California, the Edythe L. Broad Women's Heart Research Fellowship, Cedars-Sinai Medical Center, Los Angeles, California, the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, the Society for Women's Health Research (SWHR), Washington, D.C., and the Linda Joy Pollin Women's Heart Health Program, Cedars-Sinai Heart Institute, Los Angeles, California.

References

1. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ*. 1994; 308:883–6. [PubMed: 8173366]
2. Mieres JH, Shaw LJ, Arai A, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005; 111:682–96. [PubMed: 15687114]
3. Kemp HG Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol*. 1973; 32:375–6. [PubMed: 4725594]
4. Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. *J Am Coll Cardiol*. 1995; 25:807–14. [PubMed: 7884081]
5. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW. Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. *Coronary Artery Surgery Study*. *J Am Coll Cardiol*. 1995; 25:1000–9. [PubMed: 7897108]
6. Lin FY, Shaw LJ, Dunning AM, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. *J Am Coll Cardiol*. 2011; 58:510–9. [PubMed: 21777749]
7. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006; 47:S4–S20. [PubMed: 16458170]
8. Cannon RO 3rd, Epstein SE. "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol*. 1988; 61:1338–43. [PubMed: 3287885]

9. Cannon RO 3rd. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. *J Am Coll Cardiol*. 2009; 54:877–85. [PubMed: 19712795]
10. Noel Bairey Merz C, Eteiba W, Pepine C, ohnson BD, Shaw L, Kelsey S. Cardiac syndrome X: Relation to microvascular angina and other conditions. *Current Cardiovascular Risk Reports*. 2007; 1:167–75.
11. Kaski JC. Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X). *Circulation*. 2004; 109:568–72. [PubMed: 14769677]
12. Opher D, Zebe H, Weihe E, et al. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation*. 1981; 63:817–25. [PubMed: 7471337]
13. Richardson PJ, Livesley B, Oram S, Olsen EG, Armstrong P. Angina pectoris with normal coronary arteries. Transvenous myocardial biopsy in diagnosis. *Lancet*. 1974; 2:677–80. [PubMed: 4142958]
14. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007; 356:830–40. [PubMed: 17314342]
15. Vaccarino V, Badimon L, Corti R, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc Res*. 2011; 90:9–17. [PubMed: 21159671]
16. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation*. 1998; 97:2110–6. [PubMed: 9626170]
17. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002; 86:1007–13. [PubMed: 12185128]
18. Camici PG, Gistri R, Lorenzoni R, et al. Coronary reserve and exercise ECG in patients with chest pain and normal coronary angiograms. *Circulation*. 1992; 86:179–86. [PubMed: 1617771]
19. 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. [PubMed: 1939947]
20. Lanza GA, Buffon A, Sestito A, et al. Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol*. 2008; 51:466–72. [PubMed: 18222358]
21. Khuddus MA, Pepine CJ, Handberg EM, et al. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol*. 2010; 23:511–9. [PubMed: 21029178]
22. Erbel R, Ge J, Bockisch A, et al. Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris. *Eur Heart J*. 1996; 17:880–9. [PubMed: 8781827]
23. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *Journal of the American College of Cardiology*. 1986; 7:479–83. [PubMed: 3512658]
24. Bemiller CR, Pepine CJ, Rogers AK. Long-term observations in patients with angina and normal coronary arteriograms. *Circulation*. 1973; 47:36–43. [PubMed: 4686602]
25. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *Journal of the American College of Cardiology*. 1995; 25:1013–8. [PubMed: 7897110]
26. Vermeltfoort IA, Teule GJ, van Dijk AB, Muntinga HJ, Raijmakers PG. Long-term prognosis of patients with cardiac syndrome X: a review. *Netherlands heart journal: monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*. 2012; 20:365–71.
27. Gulati M, Cooper-DeHoff RM, McClure C, et al. 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. *Archives of internal medicine*. 2009; 169:843–50. [PubMed: 19433695]

28. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *European heart journal*. 2012; 33:734–44. [PubMed: 21911339]
29. Humphries KH, Pu A, Gao M, Carere RG, Pilote L. Angina with “normal” coronary arteries: sex differences in outcomes. *Am Heart J*. 2008; 155:375–81. [PubMed: 18215611]
30. Sedlak TL, Lee M, Izadnegahdar M, Merz CN, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. *Am Heart J*. 2013; 166:38–44. [PubMed: 23816019]
31. Johnston N, Schenck-Gustafsson K, Lagerqvist B. Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain? *European heart journal*. 2011; 32:1331–6. [PubMed: 21317147]
32. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women’s Ischaemia Syndrome Evaluation (WISE) study. *European heart journal*. 2006; 27:1408–15. [PubMed: 16720691]
33. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. *Circulation*. 2004; 109:2518–23. [PubMed: 15136498]
34. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000; 101:948–54. [PubMed: 10704159]
35. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008; 29:932–40. [PubMed: 18334475]
36. 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; 343:16–22. [PubMed: 10882764]
37. Eriksson BE, Tyni-Lenne R, Svedenhag J, et al. Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *J Am Coll Cardiol*. 2000; 36:1619–25. [PubMed: 11079667]
38. Asbury EA, Kanji N, Ernst E, Barbir M, Collins P. Autogenic training to manage symptomology in women with chest pain and normal coronary arteries. *Menopause*. 2009; 16:60–5. [PubMed: 18978640]
39. Sgueglia GA, Sestito A, Spinelli A, et al. Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart*. 2007; 93:591–7. [PubMed: 17237133]
40. Kronhaus KD, Lawson WE. Enhanced external counterpulsation is an effective treatment for Syndrome X. *Int J Cardiol*. 2009; 135:256–7. [PubMed: 18590931]
41. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011; 57:1404–23. [PubMed: 21388771]
42. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2011; 27(Suppl A):S1–59. [PubMed: 21640290]
43. Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. *Eur Heart J*. 2003; 24:1999–2005. [PubMed: 14613735]
44. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac Syndrome X: role of superoxide dismutase activity. *Circulation*. 2004; 109:53–8. [PubMed: 14699004]
45. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. *Am J Cardiol*. 1999; 84:854–6. [PubMed: 10513787]
46. Sutsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *Int J Cardiol*. 1995; 52:135–43. [PubMed: 8749873]

47. Heidenreich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA*. 1999; 281:1927–36. [PubMed: 10349897]
48. Tiefenbacher CP, Friedrich S, Bleeke T, Vahl C, Chen X, Niroomand F. ACE inhibitors and statins acutely improve endothelial dysfunction of human coronary arterioles. *Am J Physiol Heart Circ Physiol*. 2004; 286:H1425–32. [PubMed: 14644762]
49. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol*. 2002; 90:974–82. [PubMed: 12398965]
50. Pauly DF, Johnson BD, Anderson RD, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: A double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2011; 162:678–84. [PubMed: 21982660]
51. Denardo SJ, Wen X, Handberg EM, et al. Effect of phosphodiesterase type 5 inhibition on microvascular coronary dysfunction in women: a Women's Ischemia Syndrome Evaluation (WISE) ancillary study. *Clin Cardiol*. 2011; 34:483–7. [PubMed: 21780138]
52. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med*. 1994; 330:1411–7. [PubMed: 8159194]
53. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation*. 1998; 97:2123–8. [PubMed: 9626172]
54. Schulman SP, Becker LC, Kass DA, et al. L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA*. 2006; 295:58–64. [PubMed: 16391217]
55. Cheng JW. Ranolazine for the management of coronary artery disease. *Clin Ther*. 2006; 28:1996–2007. [PubMed: 17296457]
56. Mehta PK, Goykhman P, Thomson LE, et al. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC Cardiovasc Imaging*. 2011; 4:514–22. [PubMed: 21565740]
57. Frampton J, Buckley MM, Fitton A. Nicorandil. A review of its pharmacology and therapeutic efficacy in angina pectoris. *Drugs*. 1992; 44:625–55. [PubMed: 1281076]
58. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005; 26:2529–36. [PubMed: 16214830]
59. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009; 54:1561–75. [PubMed: 19833255]

Figure 1.

Model of Microvascular Angina in Women. HTN=hypertension, PCOS=polycystic ovary syndrome (reprinted with permission from Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. Journal of the American College of Cardiology 2009;54:1561-75⁵⁹)).

Figure 2.

Cascade of Mechanisms and Manifestations of Ischemia Impacting IHD Risk in Women (reprinted with permission from Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *Journal of the American College of Cardiology* 2009;54:1561-75⁵⁹).

Figure 3.

Recommended algorithm for the management of patients with suspected microvascular coronary dysfunction.

CAD= coronary artery disease; MI= myocardial infraction

* Empiric therapy may include anti-anginals anti-platelets and/or endothelial modifying agents

Figure 4.

Freedom from Major Adverse Cardiac Events (MACE) Grouped by Sex and CAD Status (reprinted with permission from Sedlak TL, Lee M, Izadnegahdar M, Bairey Merz CN, Gao M, Humphries KH. Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease. *American Heart Journal*. 2013 Jul;166(1):38-44³⁰).

Table 1**Five Top Research Questions for Microvascular Coronary Dysfunction**

Research Question	How Questions May Be Addressed
What is the best approach for noninvasive diagnosis?	<ul style="list-style-type: none"> Compare a non-invasive modality such as CMRI to invasive CRT to determine sensitivity and specificity
What is the best intervention for symptom management?	<ul style="list-style-type: none"> Clinical Trial in symptomatic MCD women of several different anti-anginals compared to placebo monitoring response with angina questionnaires
Do various interventions reduce major adverse cardiac events?	<ul style="list-style-type: none"> Clinical trial of medications such as statins, ACEI, aspirin compared to placebo to determine whether outcomes are improved
What are novel mechanistic pathways for MCD?	<ul style="list-style-type: none"> Pathophysiological study evaluating cardiac autonomic nervous system, smooth muscle regulation, endothelial progenitor cells, cytokine balance and vascular inflammation in MCD
What are novel treatment targets for MCD?	<ul style="list-style-type: none"> Pilot clinical trials with autonomic nervous system regulation, novel smooth muscle agents, stem cell therapy and autoimmune biologics in MCD subjects

Table 2

Evidence-based Treatment of Subjects with Angina, Evidence of Myocardial Ischemia, and No Obstructive CAD*

A. Microvascular Coronary Dysfunction (MCD)
Coronary Endothelial Dysfunction
Angiotensin Converting Enzyme Inhibitors (ACE-I) ⁵⁰
Angiotensin Receptor Blockers (if ACE-I intolerant)
HMG CoA Reductase Inhibitors (Stating) ^{43, 44}
Anti-Platelet Agent (Aspirin) ⁴¹
Enhanced External Counterpulsation (EECP) ⁴⁰
Diminished Coronary Blood Flow Reserve
Beta-blockers (including α - β blockers) ⁴⁵
L-arginine supplementation ⁵³
Coronary Smooth Muscle Dysfunction
Calcium Channel Blockers ⁴⁶
Nitrates
Anti-Anginal
Ranolazine ⁵⁶
Cognitive Behavioral Therapy/Autogenic training ³⁸
Tricyclic Medication ⁵²
Spinal Cord Stimulation (TENS unit) ³⁹
B. Coronary Vasospasm (Prinzmetal's Angina)
Calcium Channel Blockers
C. Abnormal Cardiac Nociception
Tricyclic Medication ⁵²
Spinal Cord Stimulation (TENS unit) ³⁹

Treatment of Angina in Subjects with Evidence of Myocardial Ischemia and No Obstructive Coronary Artery A Chapter in Braunwald (8th Edition) Disease. Puja K. Mehta MD, C. Noel Bairey Merz MD, FACC. *In Press*

* Proposed modification of existing ACC/AHA unstable angina and stable angina guidelines.