Published in final edited form as:

Curr Opin Cardiol. 2018 September ; 33(5): 506–513. doi:10.1097/HCO.0000000000000544.

Women's health: making cardiovascular disease real

Janet Wei, Chrisandra Shufelt, and C. Noel Bairey Merz

Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, California, USA

Abstract

Purpose of review—When patients are seen for persistent chest pain in the absence of obstructive coronary artery disease, the physician must decide if the symptoms are due to myocardial ischemia in order to guide treatment.

Recent findings—Recent findings indicate that ischemia due to coronary microvascular dysfunction (CMD) is associated with subclinical coronary atherosclerosis and an adverse prognosis. Therapeutic probe trials suggest that antiatherosclerotic and anti-ischemic therapeutic strategies may be useful. A large randomized clinical trial of high-intensity statin, maximally tolerated angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker and low-dose aspirin (WARRIOR NCT#03417388) is in progress.

Summary—The diagnosis of CMD should be considered in patients with persistent angina, evidence of myocardial ischemia and normal coronary angiogram. Because of the associated adverse prognosis of CMD, conservative empiric treatment or further diagnostic evaluation of the coronary microvasculature can be performed. Diagnosis involves the measurement of coronary blood flow in response to a vasodilator agent invasively or noninvasively. Treatment of CMD can include the use of traditional antianginal and antiatherosclerotic medications. Clinical trials are needed to assess therapeutic strategies on the outcomes of cardiovascular disease and quality of life, in order to develop evidence-based guidelines.

Keywords

cardiovascular disease; coronary microvascular dysfunction; myocardial ischemia; women

INTRODUCTION

When patients are seen for persistent chest pain in the absence of obstructive coronary artery disease (CAD), the physician must decide if the symptoms are due to myocardial ischemia. The concern is that myocardial ischemia due to coronary microvascular dysfunction (CMD) may be present, which is associated with an adverse prognosis [1–4]. Current evidence

Correspondence to C. Noel Bairey Merz, MD, FAHA, FACC, Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, 127 S. San Vicente Blvd, Suite A3206, Los Angeles, CA 90048, USA. Tel: +1 310 423 9680; fax: +1 310 423 9681; Noel.BaireyMerz@cshs.org.

Conflicts of interest

There are no conflicts of interest.

shows that a significant portion of these patients have nonobstructive coronary atherosclerosis and CMD, not evident on coronary angiography (Fig. 1) [5,6].

PROGNOSIS

Studies now have consistently shown that CMD is associated with adverse cardiovascular outcomes including death, myocardial infarction, stroke, hospitalization for angina and heart failure [7–9] (Table 1) [2,7,10[■],11–19]. Both endothelial-dependent and nonendothelial-dependent CMD predict adverse prognosis [4,20]. In the Women's Ischemia Syndrome Evaluation (WISE) study of 189 women with signs and symptoms of ischemia and no obstructive CAD, endothelial independent dysfunction characterized by reduced coronary flow reserve (CFR) is also associated with major adverse outcomes at 5-year mean follow-up (Fig. 2) [2].

The unexpectedly high heart failure hospitalizations at 4-year follow-up in these WISE individuals with preserved left ventricular (LV) ejection fraction and no obstructive CAD combined with our frequent findings of resting diastolic dysfunction (impaired LV relaxation [13,21–23] and elevated LV end-diastolic pressure (LVEDP) [13]) have led to the hypothesis that CMD represents a preheart failure with preserved ejection fraction (HfpEF) stage, contributes to diastolic dysfunction and may lead to subsequent clinical HFpEF; a condition which also preferentially impacts women. HFpEF is currently poorly understood and also lacks evidence-based therapy. Ongoing WISE study is investigating this pathophysiology.

PATHOPHYSIOLOGY

CMD encompasses various pathophysiological changes that lead to functional and structural abnormalities in the coronary microvasculature (Fig. 3) [24]. These changes disrupt the ability to vasodilate and augment blood flow in response to increased myocardial oxygen demand, causing angina and myocardial ischemia [25].

Prior WISE work has also demonstrated adverse LV remodeling in our WISE women with elevated LVEDP [26[■]]. Most recently, we have demonstrated that this does not appear to be related to blood pressure or blood pressure treatment per se, but possibly related to anti-ischemic therapy associated with improvement in angina (measured by the Seattle Angina Questionnaire) and CMD-induced ischemia measured by cardiac magnetic resonance imaging (cMRI) myocardial perfusion reserve index [27].

PATIENT CHARACTERISTICS

Patient characteristics that suggest the potential CMD should be carefully considered. Exclusion of patients with LV hypertrophy, hypertrophic cardiomyopathy, heart failure or valvular heart disease, as well as comorbidities such as anemia or thyroid dysfunction is the first step. These patients likely have secondary CMD due to obstructive CAD and should be evaluated and treated with etiologic-specific existing therapies [25].

The patients to consider evaluation for CMD include: symptoms thought by the clinician to be ischemia; evidence of ischemia by functional capacity, ECG, noninvasive stress testing or

ST-segment or non-ST-segment myocardial infarction (STEMI/NSTEMI); and no obstructive CAD by invasive or noninvasive coronary angiography [28]. The vast majority of patients have CVD risk factors and evidence of nonobstructive coronary atherosclerosis. Additional risk factors may include autoimmune conditions, cancer treatment including radiation to the chest and/or chemotherapy [29,30,31[■]].

DIAGNOSTIC STRATEGIES

Diagnostic approaches include conservative, noninvasive and invasive strategies which should involve shared decision because of the absence of guidelines in this area.

The conservative strategy includes the use of optimal medical therapy in patients at least 65 years with risk factors, including high-intensity statin, angiotensin-converting-enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB), low-dose ASA and antianginal/ anti-ischemia therapy, as well as therapeutic lifestyle change and cardiac rehabilitation [32,33]. The benefit of this strategy includes deployment of therapies known to reduce CVD risk, where the risk includes possible unnecessary overtreatment.

The noninvasive strategy involves advanced imaging using cMRI or PET to document myocardial blood flow reserve abnormality [34–36]. This strategy can be used for patients who are relatively lower risk or unable/unwilling to undergo invasive coronary reactivity testing. Because only nonendothelial function can be assessed, documentation of an abnormal flow reserve would typically be followed by nonselective optimal medical therapy and antianginal/ anti-ischemic strategies [35]. The benefit of this strategy is documentation of abnormal CFR, whereas the risks are potential false negative results because of nonresponse to pharmacologic stress and lack of specific coronary pathway to direct therapy [37].

The gold-standard test to diagnose MCD involves invasive strategies with coronary reactivity testing using intracoronary adenosine, acetylcholine and nitroglycerin to determine nonendothelial and endothelial microvascular and macrovascular coronary dysfunction pathways [38]. This strategy allows for specific pathway therapy for patients who are at higher risk because of prior STEMI, NSTEMI or resuscitated sudden cardiac death [2,3,12,37,39–42]. Other considerations for this diagnostic strategy can include lack of recognition/treatment of persistent chest pain by community physicians, repeated emergency department visits and/or coronary angiograms, lack of response to empiric therapy or uncertainty regarding the utility of optimal medical therapy in women of reproductive age [43]. The benefits of the invasive strategy include specific coronary nonendothelial, endothelial, smooth muscle and nociception pathway identification for specific therapy, whereas the risks are minimal and include traditional coronary angiography risks [38].

THERAPEUTIC STRATEGIES

Therapeutic approaches can include optimal medical therapy and therapeutic lifestyle change, and should be considered because of the presence of subclinical coronary atherosclerosis. Optimal medical therapy can consist of high-intensity statin, maximally tolerated ACE-I or ARB, β -blockers and low-dose aspirin combined with physical activity

and nutrition counseling [32,33,44–46]. Antianginal/anti-ischemic therapy can include those listed in Table 2 [44]. Pharmacologic probe and intermediate outcomes trials further support specific pathway therapies, including endothelial pathway (statins, ACE-I/ARB, aerobic exercise and external counter-pulsation therapy) [47–53], nonendothelial pathway (*a-b* blockers/*b*-blockers and ranolazine) [54–62], smooth muscle pathway [calcium channel blockers, nitrates, xanthine derivatives (aminophylline)] [63–67], cardiac nociception pathway (low-dose tricyclic medication, spinal cord stimulation and cognitive behavioral therapy) [68–72] and elevated LV filling pathway (aldosterone inhibitor, phospho-diesterase 5 inhibitors) [73–76]. Clinical trials are needed to assess therapeutic strategies on the outcomes of CVD and quality of life, in order to develop evidence-based guidelines [10¹]. Pharmacologic probe trials support an anti-atherosclerotic and anti-ischemic therapeutic approach and our ongoing clinical trial (WARRIOR NCT#03417388) is testing the impact of high-intensity statin and maximally tolerated ACE-I/ARB in 4422 CMD individuals for reduction of major adverse cardiac events (results available in 2021).

CONCLUSION

The diagnosis of CMD should be considered in patients with persistent angina, evidence of myocardial ischemia and normal coronary angiogram. Because of the associated nonobstructive coronary atherosclerosis and adverse prognosis, conservative empiric optimal medical therapy or evaluation of coronary microvasculature for the presence of CMD can be used. Diagnosis involves the measurement of CFR in response to a vasodilator agent invasively or noninvasively. Treatment of CMD can include the use of traditional antianginal and antiatherosclerotic medications. Clinical trials are needed to assess therapeutic strategies on the outcomes of CVD and quality of life, in order to develop evidence-based guidelines.

Acknowledgements

Financial support and sponsorship

This work was supported by contracts from the National Heart, Lung and Blood Institutes: N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, R01-HL 089765 and grant K23-HL-127262–01A1; a GCRC grant MO1-RR-00425 from the National Center for Research Resources; grant UL1RR033176, the NIH/ National Center for Advancing Translational Sciences (NCATS); UCLA CTSI grant UL1TR000124 and UF CTSI grant UL1TR001427; DoD contract number W81XWH-17–2–0030; 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 Constance Austin Women's Heart Research Fellowship; the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles; and the Erika J. Glazer Women's Heart Research Initiative, Cedars-Sinai Medical Center, Los Angeles.

This work was supported by grants from the Edythe L. Broad Women's Heart Research Fellowship, the Constance Austin Women's Heart Health Fellowship, the Barbra Streisand Women's Cardiovascular Research and Education Program, and the Erika J. Glazer Women's Heart Research Initiative, Cedars-Sinai Medical Center, Los Angeles.

B.M. reports personal honoraria and consulting from ACRWH (NIH Advisory Council), NIH-CASE (grant review study section), Springer International (book honorarium), Decision Support in Medicine LLC (book honorarium) and NHLBI Research Triangle Institute (RTI) International, as well as personal research grants for WISE HFpEF (Sponsor: Cedars-Sinai Medical Center, NCT02582021), RWISE (Sponsor: Cedars-Sinai Medical Center, NCT01342029), FAMRI (Sponsor: University of California, San Francisco, NCT01639235), WARRIOR Trial (Sponsor: University of Florida, NCT03417388) and California Institute for Precision Medicine (Sponsor: Cedars-Sinai Medical Center, NCT03064360). J.W. and C.S. have no disclosures to report.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

1. Bemiller CR, Pepine CJ, Rogers AK. Long-term observations in patients with angina and normal coronary arteriograms. *Circulation* 1973; 47:36–43. [PubMed: 4686602]
2. Pepine CJ, Anderson RD, Sharaf BL, et al. 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; 55:2825–2832. [PubMed: 20579539]
3. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000; 101:948–954. [PubMed: 10704159]
4. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 2004; 109:722–725. [PubMed: 14970106]
5. 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; 23:511–519. [PubMed: 21029178]
6. Schannwell CM, Steiner S, Strauer BE. Hypertensive microvascular disease. *Herz* 2005; 30:26–36. [PubMed: 15754153]
7. Britten MB, Zeiher AM, Schachinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis* 2004; 15:259–264. [PubMed: 15238822]
8. 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. *Arch Intern Med* 2009; 169:843–850. [PubMed: 19433695]
9. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; 101:1899–1906. [PubMed: 10779454]
10. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation* 2017; 135:1075–1092. [PubMed: 28289007] This scientific statement includes a summary of findings and recommendations to identify and manage patients with ischemia with no obstructive CAD. It also outlines knowledge gaps and research needs in the area.
11. Balazs E, Pinter KS, Egyed A, et al. The independent long-term prognostic value of coronary flow velocity reserve in female patients with chest pain and negative coronary angiograms (results from the SZEGED study). *Int J Cardiol* 2011; 146:259–261. [PubMed: 21129793]
12. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014; 129: 2518–2527. [PubMed: 24787469]
13. Schindler TH, Cardenas J, Prior JO, et al. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. *J Am Coll Cardiol* 2006; 47:1188. [PubMed: 16545651]
14. Rigo F, Sicari R, Gherardi S, et al. Prognostic value of coronary flow reserve in medically treated patients with left anterior descending coronary disease with stenosis 51% to 75% in diameter. *Am J Cardiol* 2007; 100:1527–1531. [PubMed: 17996513]

15. Nemes A, Forster T, Geleijnse ML, et al. Prognostic role of aortic atherosclerosis and coronary flow reserve in patients with suspected coronary artery disease. *Int J Cardiol* 2008; 131:45–50. [PubMed: 18207585]
16. Herzog BA, Husmann L, Valenta I, et al. Long-term prognostic value of N- ammonia myocardial perfusion positron emission tomography. *J Am Coll Cardiol* 2009; 54:150. [PubMed: 19573732]
17. Tio RA, Dabeshlim A, Siebelink HM, et al. Comparison between the prognostic value of left ventricular function and myocardial perfusion reserve in patients with ischemic heart disease. *J Nucl Med* 2009; 50:214–219. [PubMed: 19164219]
18. Cortigiani L, Rigo F, Gherardi S, et al. Prognostic effect of coronary flow reserve in women versus men with chest pain syndrome and normal dipyridamole stress echocardiography. *Am J Cardiol* 2010; 106:1703–1708. [PubMed: 21126613]
19. Ziadi MC, deKemp RA, Williams KA, et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol* 2011; 58:740. [PubMed: 21816311]
20. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; 106:653–658. [PubMed: 12163423]
21. Jones E, Wei J, Mehta P, et al. B-type natriuretic peptide does not correlate with invasive or noninvasive measures of coronary microvascular dysfunction in women with preserved ejection fraction: a report from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) Study. *J Am Coll Cardiol* 2014; 63(12, Supplement):A1411.
22. Nelson MD, Szczepaniak LS, Wei J, et al. Diastolic dysfunction in women with signs and symptoms of ischemia in the absence of obstructive coronary artery disease: a hypothesis-generating study. *Circ Cardiovasc Imaging* 2014; 7:510–516. [PubMed: 24633782]
23. Wei J, Nelson MD, Szczepaniak EW, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women. *Am J Physiol Heart Circ Physiol* 2016; 310: H14–H19. [PubMed: 26519031]
24. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. *Nat Rev Cardiol* 2014; 12:48. [PubMed: 25311229]
25. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007; 356:830–840. [PubMed: 17314342]
26. Elboudwarej O, Wei J, Darouian N, et al. Maladaptive remodeling may explain isolated elevated LVEDP in women with signs and symptoms of ischemia: an analysis from the WISE-CVD Study. *Int J Cardiol* 2018; In Press. This study is one of the first to suggest that in women with signs and symptoms of ischemia without obstructive CAD, isolated elevated LVEDP is associated with a significantly higher systolic and diastolic blood pressure, and left ventricle mass to volume ratio, suggesting these women have maladaptive remodeling to blood pressure. These findings are important and hypothesis generating given the higher prevalence of HFpEF in women.
27. Wei J, Thomson L, Petersen J, et al. Angina and myocardial perfusion improve in women with coronary microvascular dysfunction at 1 year follow-up: a report from the Women's Ischemia Syndrome Evaluation. *J Am Coll Cardiol* 2015; 65(10, Supplement):A1579.
28. Cannon RO 3rd. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. *J Am Coll Cardiol* 2009; 54:877–885. [PubMed: 19712795]
29. Garcia M, Mulvagh SL, Merz CN, et al. Cardiovascular disease in women: clinical perspectives. *Circ Res* 2016; 118:1273–1293. [PubMed: 27081110]
30. Ishimori ML, Martin R, Berman DS, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *JACC Cardiovasc Imaging* 2011; 4:27–33. [PubMed: 21232700]
31. Yusuf SW, Venkatesulu BP, Mahadevan LS, Krishnan S. Radiation-induced cardiovascular disease: a clinical perspective. *Front Cardiovasc Med* 2017; 4:66. [PubMed: 29124057] This article highlights the impact of radiation to the chest wall and thoracic area and the effects of unintentional irradiation to the heart which can result in fibrosis, ischemia and cardiovascular disease. It describes the pathophysiology and clinical manifestations of radiation therapy to the heart and recommendations for surveillance.

32. Marinescu MA, Loffler AI, Ouellette M, et al. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *JACC Cardiovasc Imaging* 2015; 8:210–220. [PubMed: 25677893]
33. Samim A, Nugent L, Mehta PK, et al. Treatment of angina and microvascular coronary dysfunction. *Curr Treat Options Cardiovasc Med* 2010; 12:355–364. [PubMed: 20842559]
34. Sharif B, Dharmakumar R, LaBounty T, et al. Towards elimination of the darkrim artifact in first-pass myocardial perfusion MRI: removing Gibbs ringing effects using optimized radial imaging. *Magn Reson Med* 2014; 72:124–136. [PubMed: 24030840]
35. Shufelt CL, Thomson LE, Goykhman P, et al. Cardiac magnetic resonance imaging myocardial perfusion reserve index assessment in women with microvascular coronary dysfunction and reference controls. *Cardiovasc Diagn Ther* 2013; 3:153–160. [PubMed: 24282764]
36. Valenta I, Dilsizian V, Quercioli A, et al. Quantitative PET/CT measures of myocardial flow reserve and atherosclerosis for cardiac risk assessment and predicting adverse patient outcomes. *Curr Cardiol Rep* 2013; 15:344. [PubMed: 23397541]
37. Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. *J Nucl Med* 2011; 52:726–732. [PubMed: 21498538]
38. Wei J, Mehta PK, Johnson BD, et al. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. *JACC Cardiovasc Interv* 2012; 5:646–653. [PubMed: 22721660]
39. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation* 2012; 126:1858–1868. [PubMed: 22919001]
40. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 2011; 124:2215–2224. [PubMed: 22007073]
41. Serruys PW, di Mario C, Piek J, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation* 1997; 96:3369–3377. [PubMed: 9396429]
42. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015; 131:19–27. [PubMed: 25400060]
43. Phan A, Shufelt C, Merz CN. Persistent chest pain and no obstructive coronary artery disease. *JAMA* 2009; 301:1468–1474. [PubMed: 19351944]
44. Mehta PK, Bairey Merz CN. Treatment of angina in subjects with evidence of myocardial ischemia and no obstructive coronary artery disease. Braunwald's Heart Disease 9th E-edition ed. Philadelphia, PA: Elsevier; 2011.
45. Olsen RH, Pedersen LR, Jurs A, et al. A randomised trial comparing the effect of exercise training and weight loss on microvascular function in coronary artery disease. *Int J Cardiol* 2015; 185:229–235. [PubMed: 25802037]
46. Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000; 343:16–22. [PubMed: 10882764]
47. Caliskan M, Erdogan D, Gullu H, et al. Effects of atorvastatin on coronary flow reserve in patients with slow coronary flow. *Clin Cardiol* 2007; 30:475–479. [PubMed: 17803205]
48. Eshtehardi P, McDaniel MC, Dhawan SS, et al. Effect of intensive atorvastatin therapy on coronary atherosclerosis progression, composition, arterial remodeling, and microvascular function. *J Invas Cardiol* 2012; 24:522–529.
49. Kitsou V, Xanthos T, Roberts R, et al. Enhanced external counterpulsation: mechanisms of action and clinical applications. *Acta Cardiol* 2010; 65:239–247. [PubMed: 20458834]
50. Kronhaus KD, Lawson WE. Enhanced external counterpulsation is an effective treatment for Syndrome X. *Int J Cardiol* 2009; 135:256–257. [PubMed: 18590931]
51. 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; 162:678–684. [PubMed: 21982660]
52. 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; 109:53–58. [PubMed: 14699004]
 53. Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. *Hypertension* 2000; 36:220–225. [PubMed: 10948081]
 54. Bairey Merz CN, Handberg EM, Shufelt CL, et al. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. *Eur Heart J* 2016; 37:1504–1513. [PubMed: 26614823]
 55. Hasenfuss G, Maier LS. Mechanism of action of the new antiischemia drug ranolazine. *Clin Res Cardiol* 2008; 97:222–226. [PubMed: 18046526]
 56. Hung OY, Molony D, Corban MT, et al. Comprehensive assessment of coronary plaque progression with advanced intravascular imaging, physiological measures, and wall shear stress: a pilot double-blinded randomized controlled clinical trial of nebivolol versus atenolol in nonobstructive coronary artery disease. *J Am Heart Assoc* 2016; 5:e002764. [PubMed: 26811165]
 57. 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; 84:854–856; a8. [PubMed: 10513787]
 58. Leonardo F, Fragasso G, Rossetti E, et al. Comparison of trimetazidine with atenolol in patients with syndrome X: effects on diastolic function and exercise tolerance. *Cardiologia* 1999; 44:1065–1069. [PubMed: 10687257]
 59. Matsuda Y, Akita H, Terashima M, et al. Carvedilol improves endothelium-dependent dilatation in patients with coronary artery disease. *Am Heart J* 2000; 140:753–759. [PubMed: 11054621]
 60. 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; 4:514–522. [PubMed: 21565740]
 61. Togni M, Vigorito F, Windecker S, et al. Does the beta-blocker nebivolol increase coronary flow reserve? *Cardiovasc Drugs Ther* 2007; 21:99–108. [PubMed: 17235472]
 62. Villano A, Di Franco A, Nerla R, et al. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. *Am J Cardiol* 2013; 112:8–13. [PubMed: 23558043]
 63. Cannon RO 3rd, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. *Am J Cardiol* 1985; 56:242–246. [PubMed: 4025160]
 64. Elliott PM, Krzyzowska-Dickinson K, Calvino R, et al. Effect of oral aminophylline in patients with angina and normal coronary arteriograms (cardiac syndrome X). *Heart* 1997; 77:523–526. [PubMed: 9227295]
 65. Sutsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *Int J Cardiol* 1995; 52:135–143. [PubMed: 8749873]
 66. Yesildag O, Yazici M, Yilmaz O, et al. The effect of aminophylline infusion on the exercise capacity in patients with syndrome X. *Acta Cardiol* 1999; 54:335–337. [PubMed: 10672289]
 67. Zhang X, Li Q, Zhao J, et al. Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. *Coron Artery Dis* 2014; 25:40–44. [PubMed: 24256699]
 68. Asbury EA, Kanji N, Ernst E, et al. Autogenic training to manage symptomology in women with chest pain and normal coronary arteries. *Menopause* 2009; 16:60–65. [PubMed: 18978640]
 69. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994; 330:1411–1417. [PubMed: 8159194]
 70. Cox ID, Hann CM, Kaski JC. Low dose imipramine improves chest pain but not quality of life in patients with angina and normal coronary angiograms. *Eur Heart J* 1998; 19:250–254. [PubMed: 9519318]
 71. Lanza GA, Sestito A, Sandric S, et al. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. *Italian Heart J* 2001; 2:25–30.

72. Sestito A, Lanza GA, Le Pera D, et al. Spinal cord stimulation normalizes abnormal cortical pain processing in patients with cardiac syndrome X. *Pain* 2008; 139:82–89. [PubMed: 18440702]
73. Bavry AA, Handberg EM, Huo T, et al. Aldosterone inhibition and coronary endothelial function in women without obstructive coronary artery disease: an ancillary study of the national heart, lung, and blood institute-sponsored women's ischemia syndrome evaluation. *Am Heart J* 2014; 167:826–832. [PubMed: 24890531]
74. Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction in vivo in humans: evidence for an aldosterone-induced vasculopathy. *Clin Sci* 2002; 103:425–431. [PubMed: 12241543]
75. Oestreicher EM, Martinez-Vasquez D, Stone JR, et al. Aldosterone and not plasminogen activator inhibitor-1 is a critical mediator of early angiotensin II/ NG-nitro-L-arginine methyl ester-induced myocardial injury. *Circulation* 2003; 108:2517–2523. [PubMed: 14581407]
76. Radovits T, Bomicke T, Kokeny G, et al. The phosphodiesterase-5 inhibitor vardenafil improves cardiovascular dysfunction in experimental diabetes mellitus. *Br J Pharmacol* 2009; 156:909–919. [PubMed: 19298393]

KEY POINTS

- The diagnosis of CMD should be considered in patients with persistent angina, evidence of myocardial ischemia and normal coronary angiogram.
- Diagnosis involves the measurement of CFR in response to a vasodilator agent invasively or noninvasively.
- Treatment of CMD can include the use of traditional antianginal and antiatherosclerotic medications.

FIGURE 1.

Nonobstructive coronary atherosclerosis and coronary microvascular dysfunction not visible in coronary angiography. (a) Reproduced with permissions from [5]; (c) Reproduced with permissions from [6]. Intravascular ultrasound demonstrates nonobstructive coronary atherosclerosis in a normal appearing epicardial coronary artery (panel a). Impaired coronary flow reserve to adenosine is assessed by a Doppler wire in the left anterior descending artery measuring coronary flow velocity (panel b). Model of the coronary vessels demonstrates the small vessels (diameter $<200 \mu\text{m}$) not visible in coronary angiography (panel c).

FIGURE 2.

Coronary flow reserve and event-free survival in the Women's Ischemia Syndrome Evaluation (WISE). Reproduced with permission from [24].

FIGURE 3.

Coronary microvascular dysfunction includes structural and functional abnormalities in the coronary microvasculature. Reproduced with permission from [2].

Table 1.

Prognosis in patients with chest pain and no obstructive coronary artery disease

Author, year	N	Population	Method	Outcome measure	Follow-up	CMD outcome predictor Univariate multivariate
Pepine et al. [2] (WISE)	189	Women, angina/ischemia most with nonobst CAD	Intracoronary Ado-CFR Doppler flow wire	Death, nonfatal MI, nonfatal stroke, HF hospitalization	5.4 years (mean)	Yes Yes
Balazs et al. [11] (SZEGED)	45	Women, angina/ischemia, no obstructive CAD	Vasodilator CFR, Doppler / TEE, TTE	Death, CV hospitalization	102±26 months 113 median	Yes Yes
Murthy et al. [12]	1218 813 W 405 M	No obstructive CAD (excluded by CTA or PET)	Stress perfusion imaging (PET)	CV death, MI, late revasc. (>90 days) or HF-hospitalization	3 years	Yes Yes
Britten et al. [7]	120	Post PCI/mild CAD	IC Papaverine or Ado-CFR Doppler flow wire	Cardiac death, ACS, revasc., stroke	6.5±3 years (14–125 months)	Yes Yes
Schindler et al. [13]	72	CAD risk factors without flow-limiting stenosis	CPT-MBF increase with ¹³ N-NH PET ₃	CV death, ACS, MI, PCI/CABG, stroke, PTA	66±8 months	Yes No
Rigo et al. [14]	86	CAD, LAD 51–75% stenosis	Vasodilator LAD CFR, Doppler /TTE	Nonfatal MI	30 months 14 median	Yes Yes
Nemes et al. [15]	397	Hospitalized, angina, mostly severe CAD, TEE for AA	Vasodilator LAD CFR, Doppler /TEE	CV death, HF, Thrombosis	41±12 months	Yes Yes
Herzog et al. [16]	229	Suspect CAD/66% had severe CAD	Vasodilator CFR with ¹³ N-NH PET ₃	CV death, nonfatal MI, hospitalization, PCI/CABG	5.5±2.1 years	Yes Yes
Tio et al. [17]	344	Severe CAD, not revasc. LV systolic dysfunction	Vasodilator CFR with ¹³ N-NH PET ₃	Cardiac death	85 months (1–138 months)	Yes Yes
Cortigiani et al. [18]	1660	Chest pain, normal DSE	Vasodilator LAD CFR, Doppler /TTE	Death, MI, revasc.	19 months Median	Yes Yes
Ziadi et al. [19]	677	Most had severe CAD	Vasodilator CFR with ⁸² Rb PET	CV death, nonfatal MI	387 days (375–416 days)	Yes Yes

HF, heart failure.

Reproduced with permission from [10].

Table 2.

Treatment of individuals with angina, evidence of myocardial ischemia and no obstructive coronary artery disease

Coronary microvascular dysfunction	
Abnormal endothelial function	
Angiotensin converting enzyme inhibitors	
HMG CoA reductase inhibitors (statins)	
L-arginine supplementation	
Aerobic exercise	
Enhanced external counterpulsation	
Abnormal nonendothelial function	
β -Blockers/a-b blockers	
Nitrates	
Antianginal	
Ranolazine	
Ivabradine	
Xanthine derivatives	
Abnormal smooth muscle function (prinzmetal's angina)	
Calcium channel blockers	
Nitrates	
Abnormal cardiac nociception	
Low-dose tricyclic medication	
Spinal cord stimulation	
Cognitive behavioral therapy	

Reproduced with permissions from [44].