WHITE PAPER

Ischemia and No Obstructive Coronary Artery Disease (INOCA)

Developing Evidence-Based Therapies and Research Agenda for the Next Decade

ABSTRACT: The Cardiovascular Disease in Women Committee of the American College of Cardiology, in conjunction with interested parties (from the National Heart, Lung, and Blood Institute, American Heart Association, and European Society of Cardiology), convened a working group to develop a consensus on the syndrome of myocardial ischemia with no obstructive coronary arteries. In general, these patients have elevated risk for a cardiovascular event (including acute coronary syndrome, heart failure hospitalization, stroke, and repeat cardiovascular procedures) compared with reference subjects and appear to be at higher risk for development of heart failure with preserved ejection fraction. A subgroup of these patients also has coronary microvascular dysfunction and evidence of inflammation. This document provides a summary of findings and recommendations for the development of an integrated approach for identifying and managing patients with ischemia with no obstructive coronary arteries and outlines knowledge gaps in the area. Working group members critically reviewed available literature and current practices for risk assessment and state-of-the-science techniques in multiple areas, with a focus on next steps needed to develop evidence-based therapies. This report presents highlights of this working group review and a summary of suggested research directions to advance this field in the next decade.

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STATE OF THE ART

Patients presenting with the syndrome of symptoms and signs suggesting ischemic heart disease but found to have no obstructed coronary arteries (INOCA) are increasingly recognized.[1–4] Specifically, these patients most often have symptoms suspected to be due to ischemia, prompting coronary angiography, yet no obstructive coronary artery disease (CAD), that is, ≥50% diameter stenosis, is found. Considerable evidence now documents that this syndrome is associated with a prognosis that is clearly not benign, yet no clinical practice management guidelines exist for these patients. Although there is likely overlap between INOCA and myocardial infarction (MI) with no obstructive coronary arteries (MINOCA), which appears to be increasingly described,[5–7] the primary need and focus is on non-MI syndromes. To summarize current knowledge and to provide the next steps for developing evidence-based management strategies for INOCA, a think tank was convened at the American College of Cardiology Heart House, Washington, DC, on May 17, 2016. This report summarizes those presentations and discussions.

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PREVALENCE, COSTS, AND PROGNOSTIC SIGNIFICANCE

The American College of Cardiology-National Cardiovascular Data Registry and National Heart, Lung and Blood Institute–sponsored WISE (Women's Ischemic Syndrome Evaluation) databases suggest that at least 3 to 4 million women and men with signs/symptoms suggestive of myocardial ischemia have no obstructive CAD.[8,9] Such individuals incur healthcare costs and disabilities similar to those incurred by many with obstructive CAD, in part because of angina and heart failure (HF) hospitalizations and repeat testing.[8,10] These cost burdens related to hospitalizations and repeat angiography are confirmed by a European consecutive-patient registry.[11]

Cardiovascular disease (CVD) is the leading cause of death in Americans. Although more women than men die annually of CVD, predominantly ischemic heart disease,[12] women presenting with symptoms and signs of myocardial ischemia are more likely to have no obstructive CAD on coronary angiography compared with men in the setting of both chronic and acute coronary syndromes (ACS).[4,8,13,14] Such patients are often reassured but offered no specific management, yet data now document a heightened risk of adverse CVD outcomes compared with age- and sex-matched reference subjects.[2,10,15]

Almost two thirds of women undergoing clinically indicated coronary angiography for suspected ischemic heart disease in the original cohort of the WISE had INOCA.[8,13] During follow-up, they had an intermediate risk for major adverse cardiac event (MACE; death, nonfatal MI, nonfatal stroke, and HF hospitalization) rate exceeding 2.5% yearly by 5 years, as well as elevated rates of readmission and repeat angiography triggered by symptom burden.[10,16] At 10 years, CVD death or MI occurred in 6.7% of those with no evident angiographic CAD and in 12.8% among those with nonobstructive CAD.[17] Of note, women with INOCA are ≈4 times more likely than men to be readmitted within 180 days for ACS/chest pain.[16] Large, consecutive-case registry reports have replicated this heightened risk for adverse prognosis and extended the findings to men.[2,3,18] Given the increased economic role women play in society, it is imperative to many stakeholders (Health and Human Services, Department of Labor, Department of Defense) that we understand and manage this epidemic to avoid direct and indirect economic burden (missed work, disability, death).

PREDICTORS OF ADVERSE OUTCOMES

Older age, hypertension, diabetes mellitus, and smoking have been associated with increased mortality, whereas sex, hyperlipidemia, family history of premature CAD, or pretest CAD likelihood have not.[19] Risk-adjusted analyses found that nonobstructive CAD conferred increased mortality risk compared with patients with no evident CAD.[19]

Chest pain persisting at the 1-year follow-up predicted MACE among those with INOCA in the WISE.[20] Measures of nonobstructive CAD extent and severity (WISE CAD severity score, number of vessels involved, etc) also appear important in prognosis, but these measures are not well developed.[2,3,17] A large cohort undergoing coronary computed tomographic angiography, with patients propensity matched for age, CAD risk factors, and "angina typicality," observed elevated death/MI rates in those with nonobstructive CAD versus those with normal angiograms.[21]

PATHOPHYSIOLOGY

Mechanisms contributing to INOCA appear multifactorial and may operate alone or in combination.[22,23] Although these may include hypertension, severe aortic stenosis, severe anemia, type II MI, shunts, certain drugs, HF or cardiogenic shock, Prinzmetal variant angina (coronary spasm), myocardial diseases (eg, myocarditis), congenital heart disease, coronary anomalies, myocardial bridging, and other causes in an occasional patient, underlying mechanisms and appropriate diagnostic and management strategies in these settings are usually apparent. Accordingly, the remainder of this document focuses on clinical situations in which the pathophysiological mechanism for INOCA remains unclear after initial evaluation.

Mechanisms of Coronary Flow Regulation

Coronary blood flow is closely linked with metabolite production, which modulates vascular smooth muscle tone. Voltage-gated potassium channels (Kv1.5) are critical in coupling myocardial blood flow to myocardial metabolism. Table 1 summarizes intrinsic mechanisms of coronary blood flow regulation.

Coronary Microvascular Dysfunction

One proposed mechanism contributing to INOCA is coronary microvascular dysfunction (CMD),[24] defined as epicardial, microvascular endothelial, or nonendothelial dysfunction that limits myocardial perfusion, most often detected as reduced coronary flow reserve (CFR). CMD may occur in the absence of obstructive CAD and myocardial diseases, in myocardial diseases, or in obstructive CAD or may be iatrogenic.[24] Coronary vasomotor dysfunction, even without flow-limiting stenosis, identifies patients at risk for cardiac death.[25–27] There is a distribution of risk across the CFR range from those with angiographic obstructive disease to those with diffuse nonobstructive atherosclerosis to

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Table 1. Intrinsic Mechanisms of Coronary Artery Vasoreactivity

Factor	Arteries (Endothelial Dysfunction)	Arterioles (Endothelial Dysfunction)
Serotonin	Constricts	Dilates (constricts)
Vasopressin	Dilates (±constricts)	Constricts
Endothelin	Constricts	Constricts
Thromboxane	Constricts	Constricts
Acetylcholine	Dilates (constricts)	Dilates (±constricts)
Adenosine	Dilates	Potent dilator
Nitric oxide	Dilates	Dilates
H_2O_2	Dilates	Potent dilator
Norepinephrine	Constricts	No direct effect

those with normal-appearing angiograms to those with only coronary microvascular dysfunction. There is limited correlation between anatomic CAD severity and functional impairment, as reflected in the CFR.[28] Patients with low CFR, independent of angiographic severity of obstructive disease, have increased risk for adverse outcomes. For example, diabetic patients without obstructive CAD but with impaired CFR experienced cardiac death rates similar to those for nondiabetic patients with CAD.[29] Prospective studies are needed to assess modifiability of CFR to therapy and its ability to reclassify patients at varying risk across the anatomic spectrum of CAD.

Coronary reactivity testing, usually with adenosine or an analog, is required to diagnose CMD. In the WISE, a CFR, defined as an invasive Doppler time-averaged peak hyperemic coronary flow velocity/resting flow velocity <2.32, best predicted adverse outcomes in women with INOCA, with a 5-year MACE rate of 27% versus 9.3% for those with a CFR ≥2.32 (P=0.01).[30] It is important to note that CFR was a continuous predictor of MACE, similar to blood pressure and low-density lipoprotein cholesterol, rather than having a step-like threshold for normal versus abnormal values. Similar findings (Table 2) have been observed in other studies that include noninvasive CFR velocity measurements by transthoracic echo Doppler or absolute measurements (in milliliters per minute per gram of myocardium) by positron emission tomography (PET).[26,31,32] The latter study provides the most definitive data on CMD and adverse outcome risk among patients with INOCA.[32] In those with CFR_{PET} <2.0, the MACE (cardiac death, MI, late revascularization, or HF hospitalization) rate was increased at 3 years compared with those with higher CFRs. A CFR of <2 was associated with 7.8% and 5.6% annualized MACE among symptomatic men and women without obstructive CAD versus 3.3% and 1.7%, respectively, for those with CFR ≥2.0.[32] It is interesting that although women make up ≈70% of the INOCA population,[41] increased risk associated with limited CFR does not appear different for women compared with men (Figure 1). A recent publication demonstrates that the excess cardiovascular risk in women relative to men is associated with severely impaired CFR, not with obstructive CAD.[42]

Age, Sex, and Other Risk Variables

Conditions associated with increased risk for CMD appear similar to those for obstructive CAD and include traditional atherosclerosis risk factors such as aging, hypertension, diabetes mellitus, and dyslipidemia.[43] Aging (see below) leads to increased arterial wall stiffness, medial thickening, and lumen enlargement, resulting in increased pulse pressure and hypertrophy of arteries leading to endothelial dysfunction, dysregulation of ventricular-aortic coupling, and subendocardial hypoperfusion, contributing to CMD.[44] Hypertension is associated with remodeling of small arteries, including coronary arteries,[45] and leads to arteriolar constriction and reduced microvascular density.[46] CMD may also be associated with diabetes mellitus[47] because chronic hyperglycemia reduces endothelium-dependent and -independent coronary vasodilator capacity.[48,49] Hypercholesterolemia may lead to CMD,[50] but higher high-density lipoprotein cholesterol and lower triglyceride levels are associated with higher microvascular flow.

Although CMD is most prevalent in midlife women, WISE data do not support a role for estrogen deficiency.[51] However, traditional CAD risk factors explained <20% of the variation in CMD in the WISE cohort.[51] Traditional risk factors are not always present in CMD, and novel risk markers such as those associated with inflammation may contribute.[51,52] There is a correlation between high-sensitivity C-reactive protein and number of ischemic episodes during ambulatory ECG monitoring.[53] C-reactive protein is increased among subjects with microvascular angina compared with control subjects, further supporting a possible role of inflammation and endothelial dysfunction in causing CMD.[54] Patients with increased high-sensitivity C-reactive protein have an attenuated rise in cerebral blood flow in response to acetylcholine.[55,56] Systemic lupus erythematosus is frequently associated with angina and CMD,[57] whereas prior breast cancer chemotherapy may also be associated with CMD.[58] CFR is reduced among patients with normal or minimally diseased coronary arteries and either systemic lupus erythematosus or rheumatoid arthritis, and prolonged systemic inflammation may also contribute to premature CAD in these patients.[59]

Conduit Vessel Stiffness

Aortic pulse wave velocity with other vessel stiffness indexes explained >50% of CFR variance in a WISE sub-

Table 2. Natural History Studies of Patients With Coronary Microvascular Dysfunction

Author and Year	n	Population	Method	Outcome Measure	Follow-Up	CMD Outcome Predictor	
						Univariate	Multivariate
Pepine et al[30] (WISE) 2010	189	Women, angina/ischemia most with nonobstructive CAD	Intracoronary Ado-CFR Doppler flow wire	Death, nonfatal MI, nonfatal stroke, HF hospitalization	5.4 y (mean)	Yes	Yes
Balázs et al[31] (Szeged) 2011	45	Women, angina/ischemia, no obstructive CAD	Vasodilator CFR, Doppler/TEE, TTE	Death, cardiovascular hospitalization	102±26 mo (median, 113)	Yes	Yes
Murthy et al[32] 2014	1218 (813 F, 405 M)	No obstructive CAD (excluded by CTA or PET)	Stress perfusion imaging (PET)	Cardiovascular death, MI, late revascularization (>90 d) or HF hospitalization	3 y	Yes	Yes
Britten et al[33] 2004	120	Post PCI/mild CAD	IC papaverine or Ado-CFR Doppler flow wire	Cardiac death, ACS, revascularization, stroke	6.5±3 y (14–125 mo)	Yes	Yes
Schindler et al[34] 2006	72	CAD risk factors without flow-limiting stenosis	CPT-MBF increase with 13N-NH_3 PET	Cardiovascular death, ACS, MI, PCI/CABG, stroke, PTA	66±8 mo	Yes	No
Rigo et al[35] 2007	86	CAD, LAD 51%–75% stenosis	Vasodilator LAD CFR, Doppler /TTE	Nonfatal MI	30 mo (median, 14)	Yes	Yes
Nemes et al[36] 2008	397	Hospitalized, angina, mostly severe CAD, TEE for AA	Vasodilator LAD CFR, Doppler /TEE	Cardiovascular death, HF, thrombosis	41±12 mo	Yes	Yes
Herzog et al[37] 2009	229	Suspected CAD/66% had severe CAD	Vasodilator CFR with 13N-NH_3 PET	Cardiovascular death, nonfatal MI, hospitalization, PCI/CABG	5.5±2.1 y	Yes	Yes
Tio et al[38] 2009	344	Severe CAD, not revascularization, LV systolic dysfunction	Vasodilator CFR with 13N-NH_3 PET	Cardiac death	85 mo (1–138 mo)	Yes	Yes
Cortigiani et al[39] 2010	1660	Chest pain, normal DSE	Vasodilator LAD CFR, Doppler/TTE	Death, MI, revascularization	19 mo median	Yes	Yes
Ziadi et al[40] 2011	677	Most had severe CAD	Vasodilator CFR with 82Rb PET	Cardiovascular death, nonfatal MI	387 d (375–416 d)	Yes	Yes

AA indicates abdominal aneurysm; ACS, acute coronary syndrome; Ado, adenosine; CABG, coronary artery bypass graft; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CPT, cold pressor test; CTA, computed tomographic angiography; DSE, dobutamine stress echocardiography; HF, heart failure; IC, intracoronary; LAD, left anterior descending coronary artery; LV, left ventricular; MBF, myocardial blood flow; MI, myocardial infarction; PCI, percutaneous coronary intervention; PET, positron emission tomography; PTA, percutaneous transluminal angioplasty; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and WISE, Women's Ischemia Syndrome Evaluation.

study.[60] Arterial stiffness is known to predict cardiovascular events beyond traditional risk factors. When arterial stiffness indexes were assessed by magnetic resonance imaging, ultrasound, and tonometry in asymptomatic subjects from the community,[61] peripheral and central pulse pressure, augmentation index, carotid-femoral pulse wave velocity, and aortic arch pulse wave velocity all increased with age, but ascending aortic strain and distensibility decreased with age. The best markers of subclinical large artery stiffening were aortic arch distensibility in younger individuals and aortic arch pulse wave velocity after age 50.[61]

Atherosclerosis

The pathophysiology of atherosclerosis has shifted from a lipid storage disease with large lipid pool thin fibrous cap atheroma (eg, rupture-vulnerable plaque) and flow-limiting plaque resulting in vessel occlusion to a more chronic inflammatory process interrupted by periods of minor plaque rupture, erosion, and distal embolism.[62] The initial phase begins early in life, as oxidant stress related to various risk conditions (genetic predisposition, elevated blood pressure, diabetes mellitus, low-density lipoprotein cholesterol, environmental factors such as tobacco) activates endothelial cells

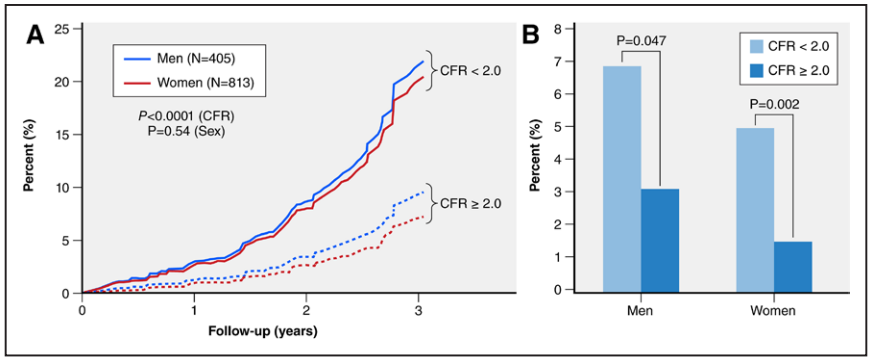

Figure 1. Sex effects on coronary microvascular dysfunction measured by positron emission tomography and adverse outcomes in symptomatic patients without obstructive coronary artery disease.
CFR indicates coronary flow reserve. Data obtained from Murthy et al.[32]

and probably vascular smooth muscle cells.[62] Bone marrow–derived inflammatory cells (monocytes) join endothelial and smooth muscle cells of the artery wall to initiate and perpetuate a less intensive, chronic inflammatory response, leading to endothelial and vascular smooth muscle dysfunction. Multiple adhesion molecules for leukocytes, chemoattractant cytokines, and activators of leukocyte function actively participate in the atherogenic process. This process is systemic with variable endothelial and vascular smooth muscle dysfunction in all vessels (large and small) and plaque growth, within large and medium-sized arteries, leading to different clinical manifestations of ischemia, depending on the acuity of the process and organs involved.[62] Evidence linking microvascular and inflammatory responses to risk factors indicates that oxidative stress, reduced nitric oxide bioavailability, and endothelial activation are common early features of coronary microvascular responses to atherosclerosis risk factors.[63]

Almost all patients with INOCA with chronic angina studied by intravascular ultrasound (IVUS) to date have some coronary atherosclerosis.[22,64] Given sampling limitations of IVUS as used in these reports, those findings strongly suggest that atherosclerosis is a key mediator of the syndrome. In support of this hypothesis, a greater burden of risk factors is associated with more atherosclerosis, concealed by compensatory positive remodeling, yielding diffuse nonobstructive CAD.[64] Plaque rupture by IVUS was not observed in patients with INOCA from 2 series of patients with chronic angina.[5,22,64] Two single-center reports of nonobstructive CAD presenting with ACS suggest that plaque rupture is observed in the minority: 38% of 50 women[6] and 37% of men and women.[5] The former study found that plaque ulceration was also frequent, in addition to late gadolinium enhancement with an ischemic pattern of injury.[6] The latter study found that plaque ruptures frequently appeared in more voluminous plaques with large plaque burden and positive remodeling.[5]

Nonobstructive CAD

Prior work evaluating patients suspected to have myocardial ischemia found that ≈40% of women and 8% of men had nonsignificant CAD (30%–49% stenosis).[14] The CASS registry (Coronary Artery Surgery Study) reported that 39% of women and 11% of men with angina had normal coronary arteries.[65] However, CASS lacked an angiographic core laboratory, and in a sample that was retrospectively reviewed, variation in interpretations of proximal lesions was unacceptably high.[66] Furthermore, it is unclear how many patients were retrospectively entered, enhancing survival bias to limit adverse outcome estimates.[67]

More recent analyses have linked angiographic measures of extent of nonobstructive CAD with increased risk for adverse outcomes. These include number of major vessels involved with nonobstructive CAD,[3] WISE-CAD Severity Score,[17] and TIMI (Thrombolysis in Myocardial Infarction) frame counts.[68] In a European consecutive-case registry of patients undergoing clinically indicated coronary angiography, the prevalence of nonobstructive CAD was 65% among women and 32% in men.[2] The American College of Cardiology-National Cardiovascular Data Registry prospective registry of patients undergoing clinically indicated invasive coronary angiography found that the prevalence of nonobstructive CAD was 51% in women and 32% in men.[9] Diffuse nonobstructive CAD is increasingly recognized with the more widespread use of fractional flow reserve, which may be helpful in assessing long moderate lesions. Measures from coronary computed tomographic angiography are also evolving. Except for the variables cited above, the other variables have not been studied in detail, and limited positive findings lack replication in other large cohorts.

Blood Pressure

Thickened and stiffened microvessels have poor autoregulatory capacity, allowing transmission of increased blood pressure to the microvessels.[24] Along with hydrau-

lic factors such as blood pressure level, intramural factors such as impaired coronary microvascular density and impaired myocardial perfusion likely contribute to INOCA.

Lipids

Dyslipidemia contributes to, and statin treatment improves, coronary endothelial dysfunction.[69] Additional contributing roles include myocardial ischemia-related steatosis, which appears to be mechanistically linked with impairments in ventricular relaxation in women with CMD evidenced by magnetic resonance spectroscopy.[70] Specifically, women with CMD had higher myocardial triglyceride content (0.83±0.12% versus 0.43±0.06%; P=0.025) and lower diastolic circumferential strain rate (168±12%/s versus 217±15%/s; P=0.012), with myocardial triglyceride content correlating inversely with diastolic circumferential strain rate (r=−0.779, P=0.002),[70] suggesting that CMD triggers a metabolic shift away from free fatty acids, resulting in ectopic fat deposition in cardiomyocytes. Mitochondrial functions, including reactive oxygen species signaling, apoptosis, steroid synthesis, hormonal signaling (mitochondrial estrogen receptor), and sexual dimorphism in the expression of mitochondria-related genes, may be involved.[71]

Obesity, Metabolic Syndrome, and Diabetes Mellitus

Obesity-related hypertension, cardiomyocyte hypertrophy, and impaired cardiac vascular adaptation to metabolic needs are well documented in obesity. Decreased serum adiponectin levels and impaired CFR occur in women with normal epicardial coronary arteries.[72] Insulin resistance is strongly associated with both microvascular and macrovascular coronary disorders and confers high risk for CVD morbidity and mortality (women more than men).[4,73] Coronary microvascular abnormalities are highly prevalent and worsen with progressive glucose intolerance with or without obstructive CAD, and nonobstructive CAD is highly prevalent in those with diabetes mellitus.[34,74,75]

Cardiac Autonomic Nervous System

Abnormal cardiac adrenergic nerve function is well documented in patients with INOCA.[76–78] Among patients experiencing mental stress–induced angina, exposure to cold triggers angina, rest angina, or early morning angina. There is close interplay between the autonomic nervous system and endothelium whereby β-adrenergic receptor activation of vascular smooth muscle cells induces vasodilation, α-adrenergic receptor activation induces vasoconstriction, and muscarinic receptor activation induces vasoconstriction.[79,80]

An abnormal vascular response to acetylcholine may be a sign of defective bioavailable nitric oxide, prostacyclin, or excess endothelium-derived hyperpolarizing factor release, or it could be indicative of increased smooth muscle cell sensitivity to muscarinic stimulation or excessive release of endothelium-derived contracting factor, a finding in HF.[81,82] Sympathetically mediated effects of mental stress on the coronary microcirculation may also be deleterious.[83] For example, CMD after percutaneous coronary intervention is due to sympathetically mediated vasoconstriction and may be prevented or attenuated by oral pretreatment with an α_1-adrenergic antagonist.[84] Normally, increased sympathetic activity dilates coronary resistance vessels to increase myocardial blood flow, modulated at least partially by endothelium.[81]

Platelet Dysfunction or Other Coagulopathy

Platelet reactivity, in response to collagen/ADP stimulation, decreases after exercise in patients with angina, positive exercise tests, and smooth coronary arteries (eg, INOCA).[85] Flow cytometry measures at rest and exercise[86] in patients with INOCA demonstrated that increases in platelet receptor expression and leukocyte-platelet aggregate formation to ACP were consistently lower after exercise than before. These findings agree with and expand on prior work demonstrating lower whole-blood platelet reactivity to collagen/ADP in patients with INOCA after exercise, in contrast to the absence of change in control subjects and an increase in patients with CAD.[13,14] Changes in platelet receptor expression and leukocyte-platelet aggregate formation have been reported after exercise in INOCA,[86] and adenosine has been shown to inhibit ADP- and thrombin-induced monocyte-platelet aggregates in INOCA.[87]

DIAGNOSIS

Invasive Testing

CBF is driven by the pressure difference between the aorta and the capillary bed and modulated further by physical and neural factors that affect the microcirculation. Different microcirculation compartments are influenced by one main physiological mechanism to control their vascular tone with cardiac metabolism as the final determining factor. Measurement of coronary vascular function includes measurements of CBF and epicardial coronary artery diameter with endothelium-dependent probes—acetylcholine, bradykinin, substance-P, L-N^G-monomethyl arginine citrate, and shear stress—and predominantly endothelium-independent probes, adenosine and sodium nitroprusside. Doses of test agents and definitions of test findings are summarized in Tables 3 and 4, respectively, in Figure 2, and the protocol in Table 5.

Exercise, pacing-induced tachycardia, cold pressor test, and mental stress have also been used to elicit abnor-

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Table 3. Intracoronary Acetylcholine Concentration and Infusion

Prepared Concentration, mol/L (μg/mL)	Infusion Rate, mL/h	Infusion Duration, min	Infused Dose, μg
10^{-6} (0.182)	48	3	0.364
10^{-4} (18.2)	48	3	36.4
10^{-4} (18.2)	120	3	108

malities in CBF. The WISE-CVD (coronary vascular dysfunction) project data suggest a strong correlation between acetylcholine and cold pressor test coronary artery diameter changes in women.[22] Reports from invasive testing >1500 patients indicate an excellent safety record with no deaths and <1% procedure-related adverse experiences such as those observed with coronary angiography.[88–90]

Noninvasive Testing

Position Emission Tomography

PET is a highly accurate, reproducible, and modifiable procedure providing comprehensive evaluation of CBF, including perfusion, left ventricular function, and CFR. There is a strong association between impaired CFR and impaired left ventricular myocardial relaxation or elevated filling pressures that is strongest among those with cardiac troponin elevations.[91] In a study[32] of chest pain patients without CAD history, PET-assessed rest and post hyperemic flow (adenosine, dobutamine, dipyridamole) identified significant MACE predictors: Duke clinical risk score (hazard ratio, 1.06), left ventricular ejection fraction (10% increase; hazard ratio, 0.56), and CFR (hazard ratio, 0.80 for each 10% increase).

Transthoracic Echo Doppler

In another study of patients with chest pain without obstructive CAD and coronary flow velocity, by pulsed wave

Table 4. Definitions of Coronary Microvascular and Macrovascular Dysfunction

CMD Pathways	Microvascular Dysfunction	Macrovascular Dysfunction
Non–endothelium dependent	CFR in response to adenosine <2.5	Change in coronary artery diameter in response to nitroglycerin <20%
Endothelium dependent	Change in CBF in response to acetylcholine <50%	Change in coronary artery diameter in response to acetylcholine ≤0%
Coronary spasm	Chest pain+ECG changes Change in coronary artery diameter in response to acetylcholine <90%	

CBF indicates coronary blood flow; CFR, coronary flow reserve; and CMD, coronary microvascular dysfunction.

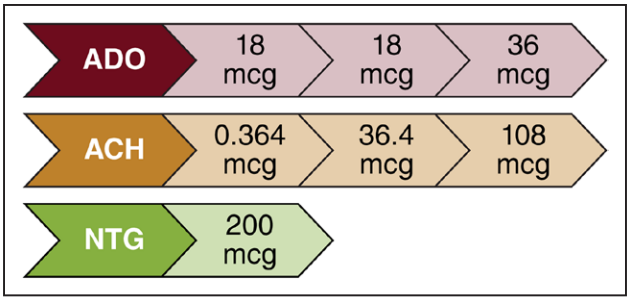

Figure 2. Coronary reactivity testing protocol.
ACH indicates acetylcholine; ADO, adenosine; and NTG, nitroglycerin.

Doppler of the left anterior descending coronary artery at rest and after dipyridamole, 26% had coronary flow velocity reserve <2.0.[92] Those with low coronary flow velocity reserve had significantly greater physical limitation and disease perception scores on the Seattle Angina Questionnaire.

Cardiac Magnetic Resonance Imaging

Failure of subendocardial perfusion to increase appropriately in response to stress can be detected by cardiac magnetic resonance imaging among subjects with INOCA.[93,94] A semiquantitative approach with measurement of myocardial perfusion reserve index detects CMD in women with INOCA.[95] Those with CMD, by abnormal invasive cardiac resynchronization therapy, had reduced myocardial perfusion reserve index compared with normal women. Because the methodology uses standard equipment and protocol available in tertiary hospitals without radiation, myocardial perfusion reserve index appears useful for the diagnosis and management of INOCA and deserves additional evaluation.

MANAGEMENT

At present, the management strategy for INOCA remains unclear, largely because of the absence of an evidence base needed for guidelines. Figure 3 outlines potential therapies for CMD.

Statins, Angiotensin-Converting Enzyme Inhibitors, and Aspirin

Multiple prior statin trials using IVUS have documented prevention of progression, or even regression, of atherosclerosis in coronary arteries and coronary endothelial or vascular smooth muscle function in subjects with nonobstructive CAD.[96,97] Statins not only lower cholesterol but also have antiatherosclerotic and anti-inflammatory effects.[98] Data support the use of statins to improve CFR. Fluvastatin alone showed improvement in CFR and even greater improvement in combination with diltiazem.[99] Two small pilot studies have shown that administration of atorvastatin improved CFR after 2 months[100] and 6 months.[101] Angiotensin-converting enzyme inhibi-

STATE OF THE ART

Table 5. Protocol for Invasive Coronary Reactivity Testing

Preparation
Withhold for 48 h
Long-acting calcium antagonists
Withhold for 24 h
Caffeine
Long-acting nitrates
Short-acting calcium antagonists
α-Blockers
β-Blockers
ACE-I/angiotensin receptor blockers/renin inhibitors/aldosterone inhibitors
Withhold for 4 h
Sublingual nitroglycerin
Protocol
Review indications for invasive coronary reactivity testing
Chest symptoms thought to be angina or equivalent
Evidence of ischemia
Confirmation of no obstructive CAD (stenosis >50%); use FFR if borderline
Assess for increased cardiac sensitivity (eg, chest pain with contrast infusion or catheter movement)
Record LVEDP
Administer intravenous heparin (70 U/kg)
Advance Doppler flow wire (0.014-in) pressure and flow system to proximal-mid LAD artery
Confirm adequate CBF velocity signal
Infuse provocative agents (using doses in Figure 2)
Recordings and calculations
12-Lead ECG, repeated with chest pain or ischemic ECG changes
APV at baseline and after each provocative agent
Hemodynamic variables (HR, BP)
Coronary angiogram for coronary artery diameter measured 5 mm distal to tip of Doppler guide wire
CBF=π(coronary artery diameter/2)2(APV/2)
CBF change=(peak CBF−baseline CBF)/(baseline CBF)

ACE-I indicates angiotensin-converting enzyme inhibitor; APV, average peak blood flow velocity; BP, blood pressure; CAD, coronary artery disease; CB, coronary blood flow; FFR, fractional flow reserve; HR, heart rate; LAD, left anterior descending; and LVEDP, left ventricular end-diastolic pressure.

tors (ACE-I) have been shown to improve exercise tolerance and angina symptoms.[102] In the WISE controlled trial, women who received quinapril had improved CFR after 16 weeks compared with the placebo group. In addition, the experimental group had improvement in angina symptoms as shown by the Seattle Angina Questionnaire.[103] Patients with essential hypertension had marked improved coronary blood flow after 12 months of treatment with perindopril, with regression of periarteriolar fibrosis seen on biopsy.[104] In patients already on an ACE-I, the addition of an aldosterone blocker did not improve endothelial function.[105] In subjects with diabetes mellitus, the addition of spironolactone has been shown to improve coronary microvascular function.[106] The benefit of spironolactone is explained by the fact that mineralocorticoid receptor activation has been shown to cause vascular damage[107] and dysfunction.[108] A statin plus ACE-I (atorvastatin and ramipril) was used in a randomized trial of angina patients with normal coronary angiograms and ischemia during stress testing; at 6 months, the statin/ACE-I strategy improved Seattle Angina Questionnaire scores and exercise duration compared with placebo. Mechanistically, the combination produced greater increases in brachial artery flow–mediated dilation compared with placebo and reduced extracellular superoxide dismutase.[102]

Antiplatelet Agents

A majority of patients with CMD have endothelial dysfunction, and although angiography shows no significant plaque burden, IVUS has demonstrated coronary atherosclerosis in most patients.[22,64] Therefore, ACC/American Heart Association chronic stable angina guidelines[109] should be extrapolated to use of antiplatelet agents such as aspirin in patients with evidence of ischemia and no obstructive CAD.

Antianginal Agents

Current approaches to the treatment of CMD (Table 6) include the management of risk factors and use of antianginal and antiatherosclerotic medication and some novel agents. However, current literature has little evidence for effective therapy for CMD for the following 2 reasons: First, studies often include patients with cardiac chest pain that may be attributed to clinical entities other than CMD such as cardiac syndrome X,[111] and second, studies have used various CFR cutoff criteria for CMD because there is no guideline consensus definition thus far.[112]

Management of risk factors includes control of diabetes mellitus and hypertension. Therapeutically lowering blood pressure can improve CFR, but excess lowering of diastolic blood pressure attenuates the benefit.[113] The insulin sensitizer metformin has been shown to improve endothelial function.[114] Lifestyle modifications include weight loss,[115] smoking cessation, high-fiber diet, fruit and vegetable consumption, and regular physical activity.[116–118]

Few studies have addressed the use of β-blockers. The existing studies included patients with signs and symptoms of ischemia but without definitive diagno-

Potential Therapies for CMD	
Pharmacologic	**Non-Pharmacologic**
• Nitrates • Statins • ACE-I • ACE-I + Aldosterone blockade • Calcium antagonists • Low-dose tricyclic antidepressants • Estrogens • PDE-5 inhibitors • Exercise • L-arginine • Ranolazine • Ivabradine • Ranolazine + Ivabradine • Metformin • Rho-kinase inhibitors • Endothelin receptor blockers	• Exercise • Cognitive behavioral therapy • Transcendental meditation • Transcutaneous electrical nerve stimulation

Figure 3. Potential therapies for coronary microvascular dysfunction (CMD).
ACE-I indicates angiotensin-converting enzyme inhibitor; and PDE-5, phosphodiesterase type 5 inhibitor.

sis of CMD. β -Blockers reduce myocardial oxygen consumption and increase diastolic filling time. Atenolol has been shown to reduce the number of angina episodes[119] and to improve ischemic threshold.[120] Carvedilol has been shown to improve endothelial function.[121]

Another class of vasodilator is calcium channel blockers, which are a reasonable first-line treatment for CMD given the underlying pathophysiology. However, one study of intracoronary diltiazem did not improve CFR in CMD patients but rather had a predominant vasodilatory effect on the epicardial artery.[122] Despite these findings, patients with abnormal vasodilator reserve can have improved symptoms, less nitrate use, and improved exercise tolerance after being treated with verapamil or nifedipine.[123]

Nitrates achieve antianginal effect through venodilation to reduce preload; in addition, they may have some coronary vasodilatory effect. The use of nitrates may improve patient symptoms, but there are limited data on their effect on endothelial and microvascular function.

Ranolazine is an antianginal that inhibits the late sodium current and overall reduces intracellular calcium levels in cardiomyocytes, thus leading to improved ventricular relaxation.[124] Results for CMD have been conflicting. One pilot study showed improved symptoms in women with angina and evidence of ischemia but no obstructive CAD, and patients with low CFR demonstrated improved CFR with treatment.[125] A similar-sized study showed some improvement with symptoms but no effect on coronary microvascular function.[126] A recent large randomized trial of a 2-week course of ranolazine versus placebo found no difference in symptoms or myocardial perfusion reserve.[127]

Ivabradine reduces heart rate through its effect on I_f of the sinoatrial node. In patients with stable CAD, it is found to improve CFR.[128] Another study showed improvement of symptoms but no effect on coronary microvascular function.[126] Ivabradine may have a therapeutic role in CMD patients.

Aminophylline, a nonselective adenosine-receptor antagonist, blocks the mediation of nociception. It is postulated to benefit CMD by attenuating the excess dilation of the microvasculature in a relatively well-perfused area, thus shunting blood to a poorly perfused area. Some improvement in symptoms and exercise capacity was seen with short-term intravenous[129] and oral aminophylline[130] in patients with signs and symptoms of ischemia but normal coronary angiogram.

Fasudil, a rho kinase inhibitor that reduces smooth muscle cell hypercontraction,[131] is being investigated currently and has potential for CMD. It has been shown to be effective for vasospastic angina. Preliminary studies showed that patients pretreated with fasudil did not manifest evidence of ischemia with acetylcholine infusion compared with saline pretreatment.[132]

There may be a role for L-arginine supplementation to improve endothelial dysfunction because L-arginine is the precursor of nitric oxide.[133] Two studies have found improvement of CFR after 1-time infusion of L-arginine.[134,135] However, Lerman et al[136] found that after 6-month oral supplementation, there is symptom improvement, decreased endothelin concentration, improvement in CBF, but no improvement in CFR.

Given that impaired cardiac nociception may be involved in CMD, low-dose tricyclic antidepressants can be considered because they are thought to have modulatory effects on norepinephrine uptake and anticholinergic effect that can cause analgesia. Imipramine has been shown to reduce frequency of pain[137,138] but in one of the studies did not show any improvement in quality of life,[138] likely because of its significant side effects.

Nonpharmacological treatments can be effective in controlling patient symptoms. Spinal cord stimulation

Table 6. Treatment of Subjects With Angina, Evidence of Myocardial Ischemia, and No Obstructive Coronary Artery Disease

CMD
Abnormal endothelial function
ACE-Is
Statins
L-arginine supplementation
Aerobic exercise
Enhanced external counterpulsation
Abnormal nonendothelial function
β-Blockers/α-blockers
Nitrates
Antianginal
Ranolazine
Ivabradine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal angina)
Calcium channel blockers
Nitrates
Abnormal cardiac nociception
Low-dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy

ACE-I indicates angiotensin converting enzyme inhibitor; and CMD, coronary microvascular dysfunction.

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has been shown to normalize abnormal pain perception,[139] to improve angina symptoms, and to increase exercise tolerance.[140] Enhanced external counterpulsation uses pneumatic cuffs applied to the patient's legs. Sequential inflation and deflation synchronized to the cardiac cycle improves hemodynamics.[141] It has been shown to improve angina in a small case series.[142] Cognitive behavioral therapy can reduce symptom severity and frequency.[143] Cardiac rehabilitation involves multiple sessions of cardiovascular exercise, psychological counseling, and nutritional planning and can be helpful in that it improves blood pressure, body mass index, and exercise capacity.[144]

In summary, small studies support the use of statins and ACE-Is to prevent the progression of nonobstructive coronary atherosclerosis and to improve endothelial and microvascular function and symptoms. However, treatments for INOCA have not been studied in clinical outcome trials adequately powered to inform evidence-based guidelines.

KNOWLEDGE GAPS

Definition

Gaps in current knowledge related to patient phenotype(s), mechanistic understanding, and management of patients with INOCA are numerous. To advance this field, it is essential to develop a uniform definition of the patient with INOCA. Prevailing elements of a definition, summarized from presentations by Think Tank members, include patients with the following:

1. Stable, chronic (several weeks or longer) symptoms suggesting ischemic heart disease such as chest discomfort with both classic (eg, angina pectoris) and atypical features in terms of location, quality, and inciting factors;
2. Objective evidence for myocardial ischemia from the ECG or a cardiac imaging study (echocardiography, nuclear imaging, magnetic resonance imaging, or spectroscopy) at rest or during stress (exercise, mental, or pharmacological); and
3. Absence of flow-limiting obstruction by coronary angiography (invasive or computed tomographic angiography) as defined by any epicardial coronary artery diameter reduction ≥50% or fractional flow reserve <0.8.

Diagnosis and Phenotyping

Given the likelihood that multiple mechanisms may contribute to INOCA, improved understanding by specific phenotyping of these individuals beyond symptoms and ischemia is needed. For example, although epicardial coronary spasm has been recognized for decades, its specific role in patients with INOCA is unclear. Although recent data suggest that ≈5% of clinically stable women with angina and INOCA have epicardial spasm with intracoronary acetylcholine testing, the role of microvascular coronary spasm requires additional study. The potential for INOCA to evolve into an ACS/MINOCA (eg, MI with no obstructive coronary arteries) or HF with preserved ejection fraction (HFpEF) requires additional study from large, prospective cohorts.

Management

Knowledge gaps exist in the pathogenesis and management of INOCA. For example, why are certain cardiovascular risk factors associated with CMD in some patients but not in others? What are the clinical, therapeutic, and prognostic implications of using a classification based on measures of nonobstructive CAD, CFR, myocardial perfusion reserve index, and PET in these patients? How often does INOCA/CMD progress to HF with preserved ejection fraction, and what is the mechanistic pathway? Are there novel provocative tests for earlier diagnosis and treatment of INOCA? The questions are numerous,

but they need to be addressed if we are to make progress in understanding and managing this common syndrome that is increasing in prevalence and costs.

RESEARCH AGENDA FOR THE NEXT DECADE

The following recommendations address 3 overarching goals: to formulate phenotypic classification of patients with INOCA based on clinical presentation, pathophysiological mechanisms, and prognosis; to develop diagnostic algorithms based on this classification system; and to develop management approaches to reduce or prevent symptoms and to modify risk for adverse outcomes.

1. Design adequately powered, population-based natural history studies/registries of patients with INOCA using consecutive-case cohorts from the large numbers of patients undergoing stress testing and coronary angiography with the definition for INOCA proposed above. Specific attention should be directed to the detection and quantification of nonobstructive atherosclerosis using invasive coronary angiography, coronary computed tomographic angiography, and other modalities. Within these studies, obtain comprehensive clinical (including detailed symptom tools such as the Seattle Angina Questionnaire, the Kansas Heart Failure Questionnaire, and other standardized quality-of-life measures) and biological information (such as functional capacity, left ventricular function, and filling pressures), including cells, tissue, and body fluids, when feasible. Collect outcomes data and develop rank-ordered adverse outcomes metrics (angina exacerbation and hospitalization, HF with preserved ejection fraction hospitalization, MI, cardiac death) in patients with INOCA.
2. Develop markers as risk reporters among high-risk patients with INOCA that include clinical and advanced technology variables (eg, proteomic, gene expression, cell-based, exosomes, miRNAs). Validate them in clinical settings and develop informatics platforms for prediction modeling that may require monitoring specific biological "signatures" periodically to discern which are perturbed before a clinical event (eg, angina, HF

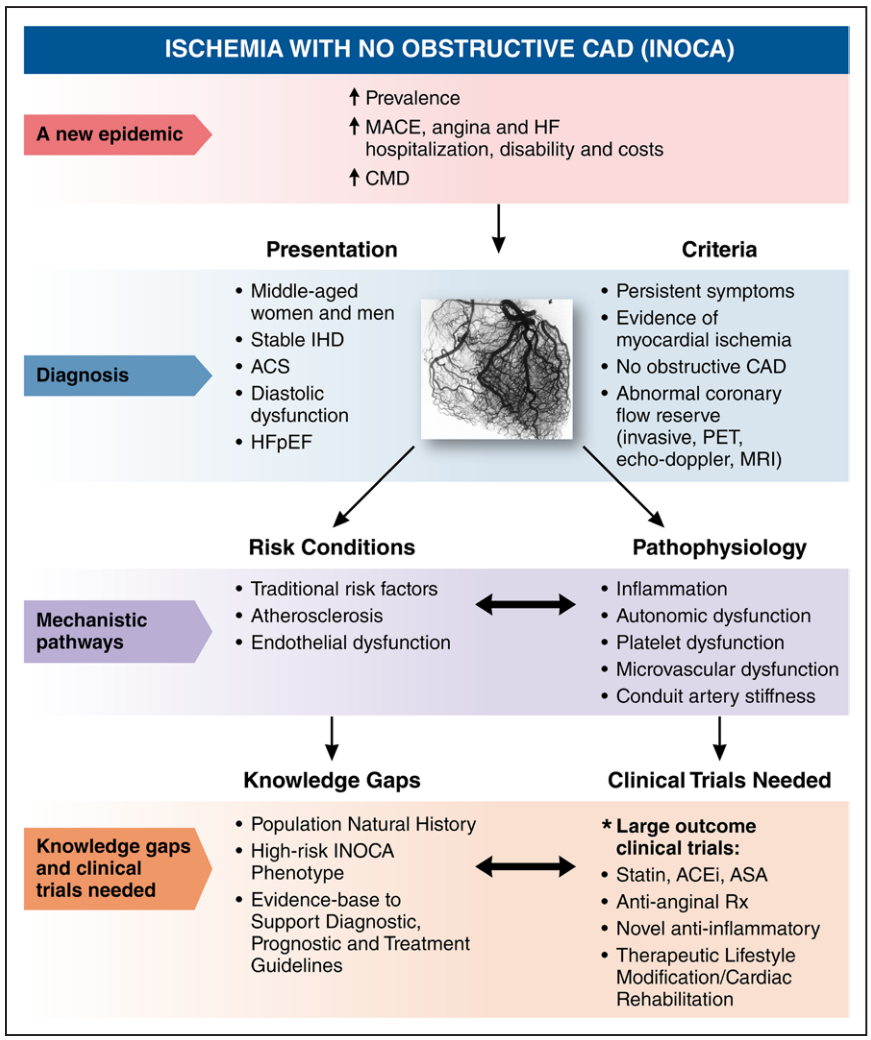

Figure 4. Ischemia with no obstructive CAD (INOCA).
ACEi indicates angiotensin-converting enzyme inhibitor; ASA, aspirin; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IHD, ischemic heart disease; MACE, major adverse cardiac event; MRI, magnetic resonance imaging; Rx, prescription; and PET, positron emission tomography.

hospitalization) and will be useful for predicting risk and directing new therapies. This should include, but not be limited to, new methods for predictive modeling using multidimensional data sets. For example, new scores could be developed and validated from coronary or computed tomographic angiography and other sources to estimate near-term risk that also include clinical and behavioral variables, existing biomarkers, genetic, 'omic, and imaging markers. The scoring system should allow the addition of new variables when they become available. It would be used as a targeted screening tool for patients deemed to be at intermediate or higher CVD risk by traditional risk scores to determine who would benefit from more intensive testing, monitoring, and therapeutic interventions. Use this information to better understand underlying pathophysiological mechanisms of INOCA, including CMD. Discover reporters for these mechanisms to investigate environmental and biological determinants that may account for individual differences in vasomotor function, plaque microdisruption, enhanced thrombus formation, sympathetic nervous system activation, and other potential triggering mechanisms for ACS.

3. Conduct adequately powered clinical trials, using standardized INOCA and CMD definitions, on risk outcomes with existing strategies effective in atherosclerotic CVD such as aspirin, statins, ACE-Is, and lifestyle modification. Conduct exploratory trials using novel interventions based on new phenotypic and mechanistic understanding on risk outcomes.
4. Construct evidence-based diagnostic and therapeutic guidelines for INOCA. Develop physician education and fellowship training programs to enhance the understanding of this syndrome and to encourage the use of novel risk assessment and management strategies. Develop programs to understand and overcome barriers to clinical implementation of these guidelines.

CONCLUSIONS

The prevalence of nonobstructive CAD among clinically ordered coronary angiograms conducted for evidence of suspected myocardial ischemia (INOCA) is increasing.[1–4] A subgroup of these patients has CMD, an elevated risk for a cardiovascular event (including ACS and repeat cardiovascular procedures), and higher risk for the development of HF hospitalization. At present, there is no uniform, comprehensive diagnostic strategy or algorithm for risk stratification for these patients; however, invasive and noninvasive CFR testing can be useful. Although small trials have suggested benefit from ACE-Is and statins, there is a lack of appropriately designed clinical outcome trials to inform evidence-based therapeutic strategies. Next steps needed to address knowledge gaps include evidence-based approaches to the definition, diagnostic evaluation, risk stratification, and management of patients with INOCA, including large outcome clinical trials. This summary of our current understanding of INOCA (Figure 4) supports the need for a research agenda for the next decade to facilitate the development of evidence-based risk assessment tools and effective therapies for this rapidly growing patient population.

APPENDIX

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FOOTNOTES

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REFERENCES

1. 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;372:1291–1300. doi: 10.1056/NEJMoa1415516.
2. 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;33:734–744. doi: 10.1093/eurheartj/ehr331.
3. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, Patel MR, Sandhu A, Valle J, Magid DJ, Leon B, Bhatt DL, Fihn SD, Rumsfeld JS. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA*. 2014;312:1754–1763. doi: 10.1001/jama.2014.14681.
4. 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;66:1918–1933. doi: 10.1016/j.jacc.2015.08.876.
5. Ouldzein H, Elbaz M, Roncalli J, Cagnac R, Carrié D, Puel J, Alibelli-Chemarin MJ. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. *Ann Cardiol Angeiol (Paris)*. 2012;61:20–26. doi: 10.1016/j.ancard.2011.07.011.
6. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, Kalhorn RT, Wood DA, Lobach IV, Hochman JS. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 2011;124:1414–1425. doi: 10.1161/CIRCULATIONAHA.111.026542.
7. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153. doi: 10.1093/eurheartj/ehw149.
8. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G; WISE Investigators. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study, part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47(suppl):S21–S29. doi: 10.1016/j.jacc.2004.12.084.
9. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, Douglas PS, Krone RJ, McKay CR, Block PC, Hewitt K, Weintraub WS, Peterson ED. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation*. 2008;117:1787–1801.
10. 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 Wom-

en's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med*. 2009;169:843–850. doi: 10.1001/archinternmed.2009.50.
11. Jespersen L, Abildstrom SZ, Hvelplund A, Madsen JK, Galatius S, Pedersen F, Hojberg S, Prescott E. Burden of hospital admission and repeat angiography in angina pectoris patients with and without coronary artery disease: a registry-based cohort study. *PLoS One*. 2014;9:e93170. doi: 10.1371/journal.pone.0093170.
12. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez 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. Heart disease and stroke statistics–2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360. doi: 10.1161/CIR.0000000000000350.
13. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, Rogers WJ, Wessel TR, Arant CB, Pohost GM, Lerman A, Quyyumi AA, Sopko G; WISE Investigators. 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(suppl):S4–S20. doi: 10.1016/j.jacc.2005.01.072.
14. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ*. 1994;308:883–886.
15. Eastwood JA, Johnson BD, Rutledge T, Bittner V, Whittaker KS, Krantz DS, Cornell CE, Eteiba W, Handberg E, Vido D, Bairey Merz CN. Anginal symptoms, coronary artery disease, and adverse outcomes in black and white women: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. *J Womens Health (Larchmt)*. 2013;22:724–732. doi: 10.1089/jwh.2012.4031.
16. Kothawade K, Bairey Merz CN. Microvascular coronary dysfunction in women: pathophysiology, diagnosis, and management. *Curr Probl Cardiol*. 2011;36:291–318. doi: 10.1016/j.cpcardiol.2011.05.002.
17. Sharaf B, Wood T, Shaw L, Johnson BD, Kelsey S, Anderson RD, Pepine CJ, Bairey Merz CN. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. *Am Heart J*. 2013;166:134–141. doi: 10.1016/j.ahj.2013.04.002.
18. 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. doi: 10.1016/j.ahj.2013.03.015.
19. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS; CONFIRM Investigators. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings: results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011;58:849–860. doi: 10.1016/j.jacc.2011.02.074.
20. Johnson BD, Shaw LJ, Pepine CJ, Reis SE, Kelsey SF, Sopko G, Rogers WJ, Mankad S, Sharaf BL, Bittner V, Bairey Merz CN. 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. *Eur Heart J*. 2006;27:1408–1415. doi: 10.1093/eurheartj/ehl040.
21. Leipsic J, Taylor CM, Gransar H, Shaw LJ, Ahmadi A, Thompson A, Humphries K, Berman DS, Hausleiter J, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chow BJ, Cury RC, Delago AJ, Dunning AL, Feuchtner GM, Hadamitzky M, Kaufmann PA, Lin FY, Chinnaiyan KM, Maffei E, Raff GL, Villines TC, Gomez MJ, Min JK. Sex-based prognostic implications of nonobstructive coronary artery disease: results from the international multicenter CONFIRM study. *Radiology*. 2014;273:393–400. doi: 10.1148/radiol.14140269.
22. 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;131:1054–1060. doi: 10.1161/CIRCULATIONAHA.114.012636.
23. Pepine CJ. Multiple causes for ischemia without obstructive coronary artery disease: not a short list. *Circulation*. 2015;131:1044–1046. doi: 10.1161/CIRCULATIONAHA.115.015553.
24. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–840. doi: 10.1056/NEJMra061889.
25. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, Renaud JM, Ruddy TD, Sarveswaran N, Tee RE, Beanlands RS. 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;58:740–748. doi: 10.1016/j.jacc.2011.01.065.
26. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124:2215–2224. doi: 10.1161/CIRCULATIONAHA.111.050427.
27. Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, Bengel FM. 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. doi: 10.2967/jnumed.110.081828.
28. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF. 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. doi: 10.1161/CIRCULATIONAHA.114.011939.
29. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, Dorbala S, Blankstein R, Di Carli MF. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation*. 2012;126:1858–1868. doi: 10.1161/CIRCULATIONAHA.112.120402.
30. 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;55:2825–2832. doi: 10.1016/j.jacc.2010.01.054.
31. Balázs E, Pintér KS, Egyed Á, Csanády M, Forster T, Nemes A. 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. doi: 10.1016/j.ijcard.2010.10.071.
32. 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;129:2518–2527. doi: 10.1161/CIRCULATIONAHA.113.008507.

33. Britten MB, Zeiher AM, Schächinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis*. 2004;15:259–264.
34. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, Sayre J, Dahlbom M, Licinio J, Schelbert HR. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. *J Am Coll Cardiol*. 2006;47:1188–1195. doi: 10.1016/j.jacc.2005.10.062.
35. Rigo F, Sicari R, Gherardi S, Djordjevic-Dikic A, Cortigiani L, Picano E. 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. doi: 10.1016/j.amjcard.2007.06.060.
36. Nemes A, Forster T, Geleijnse ML, Soliman OI, Cate FJ, Csanády M. Prognostic role of aortic atherosclerosis and coronary flow reserve in patients with suspected coronary artery disease. *Int J Cardiol*. 2008;131:45–50. doi: 10.1016/j.ijcard.2007.08.137.
37. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, Burkhard N, Wyss CA, Kaufmann PA. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J Am Coll Cardiol*. 2009;54:150–156. doi: 10.1016/j.jacc.2009.02.069.
38. Tio RA, Dabeshlim A, Siebelink HM, de Sutter J, Hillege HL, Zeebregts CJ, Dierckx RA, van Veldhuisen DJ, Zijlstra F, Slart RH. 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. doi: 10.2967/jnumed.108.054395.
39. Cortigiani L, Rigo F, Gherardi S, Galderisi M, Bovenzi F, Picano E, Sicari R. 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. doi: 10.1016/j.amjcard.2010.08.011.
40. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, Renaud JM, Ruddy TD, Sarveswaran N, Tee RE, Beanlands RS. 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;58:740–748. doi: 10.1016/j.jacc.2011.01.065.
41. Jones E, Eteiba W, Merz NB. Cardiac syndrome X and microvascular coronary dysfunction. *Trends Cardiovasc Med*. 2012;22:161–168. doi: 10.1016/j.tcm.2012.07.014.
42. Taqueti VR, Shaw LJ, Cook NR, Murthy VL, Shah NR, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Excess cardiovascular risk in women relative to men referred for coronary angiography is associated with severely impaired coronary flow reserve, not obstructive disease. *Circulation*. 2017;135:566–577. doi: 10.1161/CIRCULATIONAHA.116.023266.
43. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J*. 2014;35:1101–1111. doi: 10.1093/eurheartj/eht513.
44. Moreau P, d'Uscio LV, Lüscher TF. Structure and reactivity of small arteries in aging. *Cardiovasc Res*. 1998;37:247–253.
45. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozàkovà M, La Canna G, Nardi M, Guelfi D, Salvetti M, Morizzo C, Vittone F, Rosei EA. Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens*. 2003;21:625–631. doi: 10.1097/01.hjh.0000052467.40108.a7.
46. Smith SM, Huo T, Delia Johnson B, Bittner V, Kelsey SF, Vido Thompson D, Noel Bairey Merz C, Pepine CJ, Cooper-Dehoff RM. Cardiovascular and mortality risk of apparent resistant hypertension in women with suspected myocardial ischemia: a report from the NHLBI-sponsored WISE Study. *J Am Heart Assoc*. 2014;3:e000660. doi: 10.1161/JAHA.113.000660.
47. Sucato V, Evola S, Novo G, Novo S. Diagnosis of coronary microvascular dysfunction in diabetic patients with cardiac syndrome X: comparison by current methods [in Italian]. *Recenti Prog Med*. 2013;104:63–68. doi: 10.1701/1241.13706.
48. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol*. 1991;17:499–506.
49. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol*. 2003;41:1387–1393.
50. Kaufmann PA, Gnecchi-Ruscone T, Schäfers KP, Lüscher TF, Camici PG. Low density lipoprotein cholesterol and coronary microvascular dysfunction in hypercholesterolemia. *J Am Coll Cardiol*. 2000;36:103–109.
51. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, von Mering GO, Smith KM, Pauly DF, Handberg EM, Mankad S, Olson MB, Johnson BD, Merz CN, Sopko G, Pepine CJ; NHLBI Women's Ischemia Syndrome Evaluation (WISE). Coronary microvascular reactivity is only partially predicted by atherosclerosis risk factors or coronary artery disease in women evaluated for suspected ischemia: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). *Clin Cardiol*. 2007;30:69–74. doi: 10.1002/clc.19.
52. Recio-Mayoral A, Rimoldi OE, Camici PG, Kaski JC. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. *JACC Cardiovasc Imaging*. 2013;6:660–667. doi: 10.1016/j.jcmg.2012.12.011.
53. Cosín-Sales J, Pizzi C, Brown S, Kaski JC. C-reactive protein, clinical presentation, and ischemic activity in patients with chest pain and normal coronary angiograms. *J Am Coll Cardiol*. 2003;41:1468–1474.
54. Sakr SA, Abbas TM, Amer MZ, Dawood EM, El-Shahat N, Abdel Aal IA, Ramadan MM. Microvascular angina: the possible role of inflammation, uric acid, and endothelial dysfunction. *Int Heart J*. 2009;50:407–419.
55. Ong P, Sivanathan R, Borgulya G, Bizrah M, Iqbal Y, Andoh J, Gaze D, Kaski JC. Obesity, inflammation and brachial artery flow-mediated dilatation: therapeutic targets in patients with microvascular angina (cardiac syndrome X). *Cardiovasc Drugs Ther*. 2012;26:239–244. doi: 10.1007/s10557-012-6382-4.
56. Teragawa H, Fukuda Y, Matsuda K, Ueda K, Higashi Y, Oshima T, Yoshizumi M, Chayama K. Relation between C reactive protein concentrations and coronary microvascular endothelial function. *Heart*. 2004;90:750–754. doi: 10.1136/hrt.2003.022269.
57. Ishimori ML, Martin R, Berman DS, Goykhman P, Shaw LJ, Shufelt C, Slomka PJ, Thomson LE, Schapira J, Yang Y, Wallace DJ, Weisman MH, Bairey Merz CN. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *JACC Cardiovasc Imaging*. 2011;4:27–33. doi: 10.1016/j.jcmg.2010.09.019.
58. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc*. 2014;3:e000665. doi: 10.1161/JAHA.113.000665.
59. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. *Eur Heart J*. 2009;30:1837–1843. doi: 10.1093/eurheartj/ehp205.
60. Nichols WW, Denardo SJ, Davidson JB, Huo T, Bairey Merz CN, Pepine CJ. Association of aortic stiffness and wave reflections with coronary flow reserve in women without obstructive coronary artery disease: an ancillary study from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2015;170:1243–1254. doi: 10.1016/j.ahj.2015.08.019.

61. Redheuil A, Yu WC, Wu CO, Mousseaux E, de Cesare A, Yan R, Kachenoura N, Bluemke D, Lima JA. Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension*. 2010;55:319–326. doi: 10.1161/HYPERTENSIONAHA.109.141275.
62. Libby P, Pasterkamp G. Requiem for the "vulnerable plaque." *Eur Heart J*. 2015;36:2984–2987. doi: 10.1093/eurheartj/ehv349.
63. Vitiello L, Spoletini I, Gorini S, Pontecorvo L, Ferrari D, Ferraro E, Stabile E, Caprio M, La Sala A. Microvascular inflammation in atherosclerosis. *IJC Metab Endocr*. 2014;3:1–7.
64. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, Denardo SJ, McGorray SP, Smith KM, Sharaf BL, Nicholls SJ, Nissen SE, Anderson RD. 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. doi: 10.1111/j.1540-8183.2010.00598.x.
65. 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;25:1000–1009.
66. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C, Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KB. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). *Cathet Cardiovasc Diagn*. 1982;8:565–575.
67. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol*. 1986;7:479–483.
68. Petersen JW, Johnson BD, Kip KE, Anderson RD, Handberg EM, Sharaf B, Mehta PK, Kelsey SF, Merz CN, Pepine CJ. TIMI frame count and adverse events in women with no obstructive coronary disease: a pilot study from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). *PLoS One*. 2014;9:e96630. doi: 10.1371/journal.pone.0096630.
69. Baller D, Notohamiprodjo G, Gleichmann U, Holzinger J, Weise R, Lehmann J. Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis. *Circulation*. 1999;99:2871–2875.
70. Wei J, Nelson MD, Szczepaniak EW, Smith L, Mehta PK, Thomson LE, Berman DS, Li D, Bairey Merz CN, Szczepaniak LS. 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. doi: 10.1152/ajpheart.00612.2015.
71. Colom B, Oliver J, Garcia-Palmer FJ. Sexual dimorphism in the alterations of cardiac muscle mitochondrial bioenergetics associated to the ageing process. *J Gerontol A Biol Sci Med Sci*. 2015;70:1360–1369. doi: 10.1093/gerona/glu014.
72. Eroglu S, Sade LE, Bozbas H, Haberal A, Ozbicer S, Demir O, Muderrisoglu H. Association of serum adiponectin levels and coronary flow reserve in women with normal coronary angiography. *Eur J Cardiovasc Prev Rehabil*. 2009;16:290–296. doi: 10.1097/HJR.0b013e32831f1b8a.
73. Regensteiner JG, Golden S, Huebschmann AG, Barrett-Connor E, Chang AY, Chyun D, Fox CS, Kim C, Mehta N, Reckelhoff JF, Reusch JE, Rexrode KM, Sumner AE, Welty FK, Wenger NK, Anton B. Sex differences in the cardiovascular consequences of diabetes mellitus: a scientific statement from the American Heart Association. *Circulation*. 2015;132:2424–2447.
74. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. *J Nucl Med*. 2011;52:1369–1377. doi: 10.2967/jnumed.110.082883.
75. Nahser PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation*. 1995;91:635–640.
76. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, Agostini D, Weiland F, Chandna H, Narula J; ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure: results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol*. 2010;55:2212–2221. doi: 10.1016/j.jacc.2010.01.014.
77. Lanza GA, Giordano A, Pristipino C, Calcagni ML, Meduri G, Trani C, Franceschini R, Crea F, Troncone L, Maseri A. Abnormal cardiac adrenergic nerve function in patients with syndrome X detected by [^{123}I]metaiodobenzylguanidine myocardial scintigraphy. *Circulation*. 1997;96:821–826.
78. Mehta PK, Nelson M, Thomson L, Friedman J, Hayes S, Hermel D, Slomka P, Swift A, Wei J, Cook-Wiens G, Sayari S, Irwin MR, Krantz D, Travin M, Berman D and Bairey Merz CN. Abnormal cardiac sympathetic activity detected by 123-I-meta-iodobenzylguanidine imaging in women with signs and symptoms of ischemia and no obstructive coronary artery disease. *J Am Coll Cardiol*. 2016;67(suppl):1619.
79. Klabunde RE. *Cardiovascular Physiology Concepts*. 1st ed. Philadelphia, PA: Lippincott; 2005.
80. Muller MD, Gao Z, McQuillan PM, Leuenberger UA, Sinoway LI. Coronary responses to cold air inhalation following afferent and efferent blockade. *Am J Physiol Heart Circ Physiol*. 2014;307:H228–H235. doi: 10.1152/ajpheart.00174.2014.
81. Di Carli MF, Tobes MC, Mangner T, Levine AB, Muzik O, Chakroborty P, Levine TB. Effects of cardiac sympathetic innervation on coronary blood flow. *N Engl J Med*. 1997;336:1208–1215. doi: 10.1056/NEJM199704243361703.
82. Harris KF, Matthews KA. Interactions between autonomic nervous system activity and endothelial function: a model for the development of cardiovascular disease. *Psychosom Med*. 2004;66:153–164.
83. Dakak N, Quyyumi AA, Eisenhofer G, Goldstein DS, Cannon RO 3rd. Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease. *Am J Cardiol*. 1995;76:125–130.
84. Rimoldi O, Spyrou N, Foale R, Hackett DR, Gregorini L, Camici PG. Limitation of coronary reserve after successful angioplasty is prevented by oral pretreatment with an alpha1-adrenergic antagonist. *J Cardiovasc Pharmacol*. 2000;36:310–315.
85. Lanza GA, Andreotti F, Sestito A, Sciahbasi A, Crea F, Maseri A. Platelet aggregability in cardiac syndrome X. *Eur Heart J*. 2001;22:1924–1930. doi: 10.1053/euhj.2001.2624.
86. Lanza GA, Aurigemma C, Fattorossi A, Scambia G, Crea F. Changes in platelet receptor expression and leukocyte-platelet aggregate formation following exercise in Cardiac Syndrome X. *J Thromb Haemost*. 2006;4:1623–1625. doi: 10.1111/j.1538-7836.2006.02003.x.
87. Aurigemma C, Scalone G, Fattorossi A, Sestito A, Lanza GA, Crea F. Adenosine inhibition of adenosine diphosphate and thrombin-induced monocyte-platelet aggregates in cardiac syndrome X. *Thromb Res*. 2009;124:116–120. doi: 10.1016/j.thromres.2008.12.041.
88. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, Hill S, Schäufele T, Mahrholdt H, Kaski JC, Sechtem U. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation*. 2014;129:1723–1730. doi: 10.1161/CIRCULATIONAHA.113.004096.

89. Reriani M, Sara JD, Flammer AJ, Gulati R, Li J, Rihal C, Lennon R, Lerman LO, Lerman A. Coronary endothelial function testing provides superior discrimination compared with standard clinical risk scoring in prediction of cardiovascular events. *Coron Artery Dis*. 2016;27:213–220. doi: 10.1097/MCA.0000000000000347.
90. Wei J, Mehta PK, Johnson BD, Samuels B, Kar S, Anderson RD, Azarbal B, Petersen J, Sharaf B, Handberg E, Shufelt C, Kothawade K, Sopko G, Lerman A, Shaw L, Kelsey SF, Pepine CJ, Merz CN. 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. doi: 10.1016/j.jcin.2012.01.023.
91. Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. *Circulation*. 2015;131:528–535. doi: 10.1161/CIRCULATIONAHA.114.009716.
92. Mygind ND, Michelsen MM, Pena A, Frestad D, Dose N, Aziz A, Faber R, Høst N, Gustafsson I, Hansen PR, Hansen HS, Bairey Merz CN, Kastrup J, Prescott E. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER Study. *J Am Heart Assoc*. 2016;5:e003064. doi: 10.1161/JAHA.115.003064.
93. Lanza GA, Buffon A, Sestito A, Natale L, Sgueglia GA, Galiuto L, Infusino F, Mariani L, Centola A, Crea F. 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;51:466–472. doi: 10.1016/j.jacc.2007.08.060.
94. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med*. 2002;346:1948–1953. doi: 10.1056/NEJMoa012369.
95. 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 and 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.
96. Ballantyne CM, Raichlen JS, Nicholls SJ, Erbel R, Tardif JC, Brener SJ, Cain VA, Nissen SE; ASTEROID Investigators. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation*. 2008;117:2458–2466. doi: 10.1161/CIRCULATIONAHA.108.773747.
97. Dupuis J, Tardif JC, Cernacek P, Théroux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes: the RECIFE (Reduction of Cholesterol in Ischemia and Function of the Endothelium) trial. *Circulation*. 1999;99:3227–3233.
98. Ridker PM, MacFadyen J, Libby P, Glynn RJ. Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Am J Cardiol*. 2010;106:204–209. doi: 10.1016/j.amjcard.2010.03.018.
99. Zhang X, Li Q, Zhao J, Li X, Sun X, Yang H, Wu Z, Yang J. Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. *Coron Artery Dis*. 2014;25:40–44. doi: 10.1097/MCA.0000000000000054.
100. Caliskan M, Erdogan D, Gullu H, Topcu S, Ciftci O, Yildirir A, Muderrisoglu H. Effects of atorvastatin on coronary flow reserve in patients with slow coronary flow. *Clin Cardiol*. 2007;30:475–479. doi: 10.1002/clc.20140.
101. Eshtehardi P, McDaniel MC, Dhawan SS, Binongo JN, Krishnan SK, Golub L, Corban MT, Raggi P, Quyyumi AA, Samady H. Effect of intensive atorvastatin therapy on coronary atherosclerosis progression, composition, arterial remodeling, and microvascular function. *J Invasive Cardiol*. 2012;24:522–529.
102. 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. doi: 10.1161/01.CIR.0000100722.34034.E4.
103. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, Sopko G, Sharaf BM, Kelsey SF, Merz CN, Pepine CJ. 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. doi: 10.1016/j.ahj.2011.07.011.
104. 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.
105. Bavry AA, Handberg EM, Huo T, Lerman A, Quyyumi AA, Shufelt C, Sharaf B, Merz CN, Cooper-DeHoff RM, Sopko G, Pepine CJ. 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. doi: 10.1016/j.ahj.2014.01.017.
106. Garg R, Rao AD, Baimas-George M, Hurwitz S, Foster C, Shah RV, Jerosch-Herold M, Kwong RY, Di Carli MF, Adler GK. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes*. 2015;64:236–242. doi: 10.2337/db14-0670.
107. Oestreicher EM, Martinez-Vasquez D, Stone JR, Jonasson L, Roubsanthisuk W, Mukasa K, Adler GK. 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. doi: 10.1161/01.CIR.0000097000.51723.6F.
108. Farquharson CA, Struthers AD. Aldosterone induces acute endothelial dysfunction *in vivo* in humans: evidence for an aldosterone-induced vasculopathy. *Clin Sci (Lond)*. 2002;103:425–431. doi: 10.1042/.
109. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767. doi: 10.1161/CIR.0000000000000095.
110. Mehta PK, Bairey Merz, CN. Treatment of angina in subjects with evidence of myocardial ischemia and no obstructive coronary artery disease. In: *Braunwald's Heart Disease*. 9th ed. Philadelphia, PA: Elsevier; 2011.
111. Kemp HG Jr, Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms: report of a six year experience. *Am J Med*. 1973;54:735–742.

112. Marinescu MA, Löffler AI, Ouellette M, Smith L, Kramer CM, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *JACC Cardiovasc Imaging*. 2015;8:210–220. doi: 10.1016/j.jcmg.2014.12.008.
113. Mizuno R, Fujimoto S, Saito Y, Okamoto Y. Optimal antihypertensive level for improvement of coronary microvascular dysfunction: the lower, the better? *Hypertension*. 2012;60:326–332. doi: 10.1161/HYPERTENSIONAHA.111.189209.
114. Jadhav S, Ferrell W, Greer IA, Petrie JR, Cobbe SM, Sattar N. Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*. 2006;48:956–963. doi: 10.1016/j.jacc.2006.04.088.
115. Lim TK, Choy AJ, Khan F, Belch JJ, Struthers AD, Lang CC. Therapeutic development in cardiac syndrome X: a need to target the underlying pathophysiology. *Cardiovasc Ther*. 2009;27:49–58. doi: 10.1111/j.1755-5922.2008.00070.x.
116. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29:932–940. doi: 10.1093/eurheartj/ehn018.
117. 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. doi: 10.1056/NEJM200007063430103.
118. Parikh P, McDaniel MC, Ashen MD, Miller JI, Sorrentino M, Chan V, Blumenthal RS, Sperling LS. Diets and cardiovascular disease: an evidence-based assessment. *J Am Coll Cardiol*. 2005;45:1379–1387. doi: 10.1016/j.jacc.2004.11.068.
119. 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;84:854–866, A8.
120. Leonardo F, Fragasso G, Rossetti E, Dabrowski P, Pagnotta P, Rosano GM, Chierchia SL. Comparison of trimetazidine with atenolol in patients with syndrome X: effects on diastolic function and exercise tolerance. *Cardiologia*. 1999;44:1065–1069.
121. Matsuda Y, Akita H, Terashima M, Shiga N, Kanazawa K, Yokoyama M. Carvedilol improves endothelium-dependent dilatation in patients with coronary artery disease. *Am Heart J*. 2000;140:753–759. doi: 10.1067/mhj.2000.110093.
122. Sütsch 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.
123. 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.
124. Hasenfuss G, Maier LS. Mechanism of action of the new antiischemia drug ranolazine. *Clin Res Cardiol*. 2008;97:222–226. doi: 10.1007/s00392-007-0612-y.
125. Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, Yang Y, Gill E, Minissian M, Shaw LJ, Slomka PJ, Slivka M, Berman DS, Bairey Merz CN. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC Cardiovasc Imaging*. 2011;4:514–522. doi: 10.1016/j.jcmg.2011.03.007.
126. Villano A, Di Franco A, Nerla R, Sestito A, Tarzia P, Lamendola P, Di Monaco A, Sarullo FM, Lanza GA, Crea F. Effects of ivabradine and ranolazine in patients with microvascular angina pectoris. *Am J Cardiol*. 2013;112:8–13. doi: 10.1016/j.amjcard.2013.02.045.
127. Bairey Merz CN, Handberg EM, Shufelt CL, Mehta PK, Minissian MB, Wei J, Thomson LE, Berman DS, Shaw LJ, Petersen JW, Brown GH, Anderson RD, Shuster JJ, Cook-Wiens G, Rogatko A, Pepine CJ. 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. doi: 10.1093/eurheartj/ehv647.
128. Skalidis EI, Hamilos MI, Chlouverakis G, Zacharis EA, Vardas PE. Ivabradine improves coronary flow reserve in patients with stable coronary artery disease. *Atherosclerosis*. 2011;215:160–165. doi: 10.1016/j.atherosclerosis.2010.11.035.
129. Yeşildağ O, Yazici M, Yilmaz O, Uçar R, Sağkan O. The effect of aminophylline infusion on the exercise capacity in patients with syndrome X. *Acta Cardiol*. 1999;54:335–337.
130. Elliott PM, Krzyzowska-Dickinson K, Calvino R, Hann C, Kaski JC. Effect of oral aminophylline in patients with angina and normal coronary arteriograms (cardiac syndrome X). *Heart*. 1997;77:523–526.
131. Shi J, Wei L. Rho kinases in cardiovascular physiology and pathophysiology: the effect of fasudil. *J Cardiovasc Pharmacol*. 2013;62:341–354. doi: 10.1097/FJC.0b013e3182a3718f.
132. Mohri M, Shimokawa H, Hirakawa Y, Masumoto A, Takeshita A. Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. *J Am Coll Cardiol*. 2003;41:15–19.
133. Palmer RM, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature*. 1988;333:664–666. doi: 10.1038/333664a0.
134. Egashira K, Hirooka Y, Kuga T, Mohri M, Takeshita A. Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary arteriograms. *Circulation*. 1996;94:130–134.
135. Gellman J, Hare JM, Lowenstein CJ, Gerstenblith G, Coombs V, Langenberg P, Brinker JA, Resar JR. L-Arginine ameliorates the abnormal sympathetic response of the dysfunctional human coronary microvasculature. *Angiology*. 2004;55:1–8.
136. 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;97:2123–2128.
137. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, Geraci MF, Black BC, Uhde TW, Waclawiw MA. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med*. 1994;330:1411–1417. doi: 10.1056/NEJM199405193302003.
138. 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.
139. Sestito A, Lanza GA, Le Pera D, De Armas L, Sgueglia GA, Infusino F, Miliucci R, Tonali PA, Crea F, Valeriani M. Spinal cord stimulation normalizes abnormal cortical pain processing in patients with cardiac syndrome X. *Pain*. 2008;139:82–89. doi: 10.1016/j.pain.2008.03.015.
140. Lanza GA, Sestito A, Sandric S, Cioni B, Tamburrini G, Barollo A, Crea F, De Seta F, Meglio M, Bellocci F, Maseri A. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. *Ital Heart J*. 2001;2:25–30.
141. Kitsou V, Xanthos T, Roberts R, Karlis GM, Padadimitriou L. Enhanced external counterpulsation: mechanisms of action and clinical applications. *Acta Cardiol*. 2010;65:239–247. doi: 10.2143/AC.65.2.2047060.
142. Kronhaus KD, Lawson WE. Enhanced external counterpulsation is an effective treatment for Syndrome X. *Int J Cardiol*. 2009;135:256–257. doi: 10.1016/j.ijcard.2008.03.022.
143. 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;16:60–65. doi: 10.1097/GME.0b013e318184762e.
144. Samim A, Nugent L, Mehta PK, Shufelt C, Bairey Merz CN. Treatment of angina and microvascular coronary dysfunction. *Curr Treat Options Cardiovasc Med*. 2010;12:355–364. doi: 10.1007/s11936-010-0083-8.