1-29-2022

Coronary Microvascular Dysfunction in Patients with Non-Obstructive Coronary Arteries: Current Gaps and Future Directions

Islam Y. Elgendy

Lina Ya'qoub
Henry Ford Health, lyaqou1@hfhs.org

Kuan-Han Chen

Carl J. Pepine

Drugs
https://doi.org/10.1007/s40265-021-01667-y

LEADING ARTICLE

Coronary Microvascular Dysfunction in Patients with Non-Obstructive Coronary Arteries: Current Gaps and Future Directions

Islam Y. Elgendy[1] · Lina Ya'Qoub[2] · Kuan-Han Chen[1] · Carl J. Pepine[3]

Accepted: 16 December 2021

Abstract

There has been increasing interest in open artery syndrome, also known as ischemia with non-obstructive coronary arteries (INOCA). INOCA has been increasingly recognized as a heterogeneous clinical entity. Diagnostic evaluation of this heterogeneous entity, including invasive assessment, remains key to diagnose this clinical condition and provide the appropriate treatment. Importantly, medical stratification based on the type of INOCA has shown benefit in improving the symptoms in these patients, as illustrated in the CorMicA trial. The *W*omen's Ischemi*A* Trial to *R*educe Events in Non-Obst*R*uct*I*ve C*OR*onary Artery Disease (WARRIOR) is another promising landmark trial that is currently enrolling patients and will address some of the unanswered questions for management of women with INOCA. In this review, we discuss the pathophysiology, management options, knowledge gaps, and future directions while highlighting the rationale and design of the ongoing WARRIOR trial.

Key Points

Ischemia with non-obstructive coronary arteries (INOCA) is increasingly recognized as a heterogeneous clinical entity.

Coronary microvascular dysfunction (CMD) is divided into two sub-types: structural and functional.

Medical therapy stratification based on INOCA sub-type demonstrated improvement in angina in these patients, as shown in the CorMicA trial.

The WARRIOR is an ongoing landmark trial randomizing patients with INOCA to intensive medical treatment versus usual care and assessing the impact on clinical outcomes.

Islam Y. Elgendy and Lina Ya'Qoub equally contributed as first co-authors.

✉ Carl J. Pepine
carl.pepine@medicine.ufl.edu

[1] Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar

[2] Department of Interventional Cardiology, Henry Ford Hospital, Detroit, MI, USA

[3] Division of Cardiovascular Medicine, University of Florida, 1329 SW 16th St, PO Box 100288, Gainesville, FL 32610, USA

1 Introduction

Coronary artery disease (CAD) remains a leading cause of death and disability in the USA and worldwide, even among women [1]. Traditionally, CAD has been mechanistically linked with a flow-limiting stenosis in an epicardial coronary artery due to obstruction caused by atherosclerotic plaque. There has been growing interest in the entity of non-obstructive CAD (i.e., epicardial coronary artery stenosis <50% diameter or non-flow–limiting), which is very frequent among patients presenting with symptoms and/or signs of myocardial ischemia [2–5]. Clinically, these findings may be defined together as "open artery ischemia" or ischemia with no obstructive coronary arteries (INOCA). This syndrome is often a direct result of inadequate coronary perfusion due to limitations of the microvasculature to appropriately match blood flow with myocardial oxygen demands [2–5]. Although previously viewed as "benign", recognition of INOCA has become relevant since accumulating evidence documents an elevated risk for poor quality of life, major adverse cardiac event (MACE), and also burdens on the healthcare system with few promising treatments at present [3, 5–9].

2 Epidemiology

INOCA is not an uncommon condition. In an analysis from the National Cardiovascular Data Registry's CathPCI Registry of 661,063 patients undergoing elective coronary

Published online: 29 January 2022

angiography, the majority (58.4%) had evidence of non-obstructive CAD [8]. Patients with non-obstructive CAD were younger, more likely to be women, and obese or overweight. In addition, the prevalence of traditional cardiovascular risk factors such as diabetes mellitus and hypertension were comparable to groups with obstructive CAD [8, 9]. In a Danish study of 11,223 patients with stable angina pectoris, 15.2% had non-obstructive CAD. Non-obstructive CAD was associated with a 52% excess risk for all-cause mortality (hazards ratio [HR] 1.52, 95% confidence interval [CI] 1.24–1.88) and MACE (HR 1.52, 95% CI 1.24–1.88) compared with a reference population without ischemic heart disease [4]. These findings were further supported by another study of 37,674 veterans which showed that non-obstructive CAD was associated with increased risk of all-cause mortality and myocardial infarction at 1 year, which was exacerbated by increasing numbers of vessels affected with non-obstructive CAD [2]. It is important to note that the risk of MACE increased with increasing degrees of CAD (HR 1.52, 95% CI 1.27–1.83) among patients with INOCA and normal coronary arteries as well as patients with diffuse non-obstructive CAD (HR 1.85, 95% CI 1.51–2.28). For all-cause mortality, normal coronary arteries and diffuse non-obstructive CAD were associated with HRs of 1.29 (1.07–1.56) and 1.52 (1.24–1.88), respectively [4].

3 Pathophysiology of INOCA and Potential Targets for Management

INOCA was defined by a consensus statement from the European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation, which was also endorsed by the Coronary Vasomotor Disorders International Study (COVADIS) group, as a demand-supply mismatch of coronary artery blood flow leading to transient or recurrent cardiac chest pain related to myocardial ischemia. The mismatch between blood supply and myocardial oxygen demands may be caused by coronary microvascular dysfunction and/or epicardial coronary artery spasm, typically in the setting of non-obstructive coronary atherosclerosis. In this setting, the working group provided diagnostic criteria for microvascular angina to include all of the following: (1) Symptoms of myocardial ischemia, (2) Absence of obstructive CAD (< 50% diameter reduction or FFR > 0.80), (3) Objective evidence of myocardial ischemia, and 4) Evidence of impaired coronary microvascular function [10].

The underlying mechanisms implicated in the pathophysiology for INOCA are multifactorial [9, 11]. Coronary microvascular dysfunction (CMD) remains a central component in the pathophysiology of INOCA and is defined by Camici and Crea as either coronary vascular smooth muscle dysfunction or endothelial dysfunction [12]. CMD may be broadly classified into two endotypes: structural CMD and functional CMD [13]. Structural CMD is characterized by reduced microvascular conductance and impaired oxygen delivering capacity to the myocardium. The decreased microvascular conductance is a result of inward remodeling of small-sized coronary arterioles, while the impaired oxygen delivering capacity to the myocardium is a product of myocardial capillary rarefaction or low coronary microvascular density [14]. Both inward remodeling of small-sized coronary arterioles and myocardial capillary rarefaction are commonly seen in structural CMD. Other comorbidities, such as diabetes mellitus and hypertension, have long been linked with CMD and exacerbate the detrimental effects of structural CMD [9, 15–19]. Not uncommonly, atherosclerosis is observed in a significant proportion of patients with INOCA on intravascular imaging [9, 15]. In these cases, intravascular imaging has documented that positive remodeling conceals the atherosclerotic plaque. By contrast, functional CMD does not result from inward remodeling of small-sized coronary arterioles, but rather represents an impaired flow-mediated/endothelium-dependent vasodilation of the microvasculature [13]. Coronary arterioles' insensitivity to vasodilatory stimuli and hypersensitivity to vasoconstrictive stimuli amplify, and thus diffuse stenoses in the microvasculature can be widely seen. Like structural CMD, several comorbidities are observed among patients with functional CMD. Chronic inflammation, documented by elevated high-sensitivity C-reactive protein, augments the adverse effects of structural and functional CMD and accentuates the degree of angina [20, 21]. Furthermore, cardiac, and perhaps central, autonomic nervous system activation is associated with intensification of the detrimental effects of functional CMD by impairing modulation between vasodilatory and vasoconstrictive stimuli (Fig. 1). Vasospastic angina is the clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary obstruction caused by a vasomotor disorder. Epicardial vessel spasm typically occurs when hyper-reactive epicardial coronary vessel segment undergoes maximal contraction when exposed to vasoconstrictor stimuli, which include smoking, cold weather, drugs, peaks in blood pressure, emotional stress, and hyperventilation. Concomitant vasospastic angina and CMD are associated with worse prognosis [10]. Table 1 summarizes endotypes of INOCA.

It is worth mentioning that there seems to be an association between INOCA and heart failure with preserved ejection fraction (HFpEF). Data from endomyocardial biopsy samples from patients with HFpEF showed that an inflamed microvascular endothelium allows monocyte migration and transforming growth factor (TGF)-β release that promotes the differentiation of fibroblasts into myofibroblasts,

promoting collagen production and cross-linking. Furthermore, this pro-inflammatory and pro-oxidative state may render the dysfunctional coronary microvasculature more vulnerable to repeat episodes of myocardial ischemia and micro-infarcts leading to interstitial fibrosis and shift in substrate metabolism, ultimately leading to HFpEF in humans [22–24]. We are currently investigating CMD as a pre-HFpEF syndrome (ClinicalTrials.gov NCT03876223).

4 Management of INOCA

It is important that providers and patients understand the "natural" history of INOCA patients that was recently presented in the CIAO-Ischemia ancillary study [25]. That INOCA cohort had a degree of stress inducible wall motion abnormalities similar to that of the concurrently enrolled ISCHEMIA trial participants with obstructive CAD. But despite no specific treatments, improvement in the ischemia-induced wall motion abnormalities and improvement in angina occurred in about half of INOCA patients at 1 year, but interestingly these responses were not correlated. Such results highlight the complexities of INOCA pathophysiology as well the multifactorial mechanisms of angina.

With this background, we recommend that management should be patient-centered with a multidisciplinary care approach focusing on lifestyle modification and aggressive risk factor control, including blood pressure, glycemic and lipid management, with smoking cessation and exercise/activity promotion [26]. Treatment of underlying comorbidities and avoiding known triggering factors are also key [26]. Studies have shown benefit of certain medications in this heterogenous group of patients. Table 2 summarizes the evidence supporting these medications in INOCA. While beta-blockers, calcium channel blockers, ranolazine and ivabradine may have benefit in certain patients, subgroups with impaired vasodilation and/or excessive vasoconstriction may benefit more from calcium channel blockers and/or nitrates [26–28].

Table 1 Summary of endotypes of INOCA

Endotype	Definition/characteristic
CMD	CMD is defined by Camici and Crea as either coronary vascular smooth muscle dysfunction or endothelial dysfunction. CMD may be broadly classified into two endotypes: structural CMD and functional CMD. Structural CMD is characterized by reduced microvascular conductance and impaired oxygen delivering capacity to the myocardium due to inward remodeling of small-sized coronary arterioles. By contrast, functional CMD results from an impaired flow-mediated endothelium-dependent vasodilation of the microvasculature with insensitivity to vasodilatory stimuli and hypersensitivity to vasoconstrictive stimuli amplify [10, 12, 13, 22]
Vasospastic angina	Vasospastic angina is the clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary obstruction secondary to a vasomotor disorder. Epicardial vessel spasm typically occurs when hyper-reactive epicardial coronary vessel segment undergoes maximal contraction when exposed to vasoconstrictor stimuli, which include smoking, cold weather, drugs, peaks in blood pressure, emotional stress, and hyperventilation [10, 22]

CMD coronary microvascular dysfunction

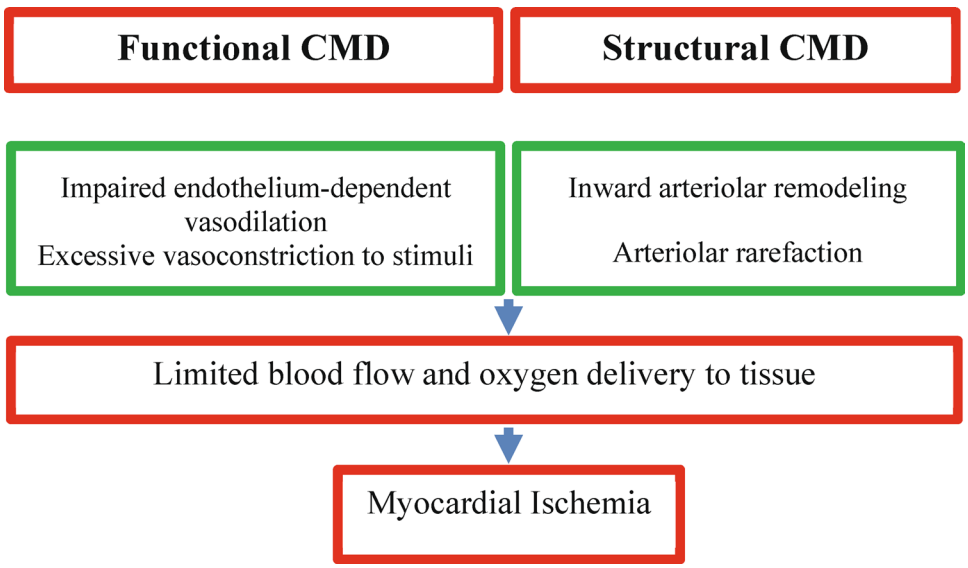

Fig. 1 Summary of endotypes of coronary microvascular dysfunction (CMD)

4.1 Conventional Therapies

Calcium channel blockers are vasodilators, which help prevent epicardial and microvascular coronary vasospasm. Verapamil, diltiazem, nifedipine, amlodipine, and nisoldipine have all decreased symptoms and increased effort tolerance in trials of INOCA patients, compared with placebo [29–32]. Their combination with a statin appeared particularly effective [30]. These results suggest that at least a subgroup of INOCA patients benefits from calcium channel blockers. However, their effect on CFR itself appears to be limited [26–28].

Nitrates, short- and long-acting, have been studied in patients with CMD with inconclusive results but there were important differences in inclusion criteria of the study population. In our experience short-acting nitrates are often effective in relieving acute chest pain in patients with CMD, especially when administered on the background of a calcium channel blocker or β-blocker. However, long-acting nitrates incompletely control symptoms in CMD patients although we continue to use them. We have observed that short-term nitroglycerin ointment with an occlusive dressing to achieve high doses may be helpful for some patients with exacerbations of resting angina to avoid hospitalization.

Beta-blockers, especially selective beta-1 blockers, including nebivolol, have vasodilatory effects via nitric oxide production, resulting in increase of CFR [33]. In a study of 18 patients, doppler-flow-wire–derived coronary flow velocity measurements were obtained in 10 controls and 8 patients with CAD at rest and after intracoronary nebivolol. In the CAD group, collateral flow was determined after dilatation of a flow-limiting coronary stenosis. The investigators found that intracoronary nebivolol increased CFR in both controls and CAD patients [33].

Ranolazine blocks late sodium channels and decreases intracellular calcium, leading to cardiomyocyte relaxation and thus, potentially improves CMD. The effect of ranolazine has been controversial; in a randomized crossover trial of 128 patients (96% were women) with evidence of CMD, confirmed using invasive coronary reactivity testing or non-invasive cardiac magnetic resonance imaging, myocardial perfusion reserve index showed no differences in symptoms or magnetic resonance perfusion reserve in the study cohort. However, in a subsequent analysis of the study based on baseline CFR on invasive testing, ranolazine showed benefit in patients with reduced CFR at baseline [34, 35].

Angiotensin converting enzyme inhibitors (ACEIs) have been shown to be beneficial in CMD by either directly affecting the vascular function through the renin-angiotensin pathway or indirectly by controlling blood pressure. ACEIs have been associated with improved CFR and intracoronary Doppler coronary flow measurements by increasing endothelial nitric oxide bioavailability [36, 37]. In a sub-study of the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE), 78 women with microvascular dysfunction (coronary flow reserve < 3.0 following adenosine) and no obstructive CAD were randomly assigned to either quinapril or a placebo treatment group. Sixty-one women completed the 16-week treatment period with repeat CFR measurements. ACEI was associated with significantly improved CFR at 16 weeks. Regarding the secondary outcome in this sub-study, which assessed symptoms of angina, both ACEIs ($p = 0.037$) and CFR increase ($p = 0.008$) contributed to symptom improvements [36].

Statins The benefit of statins comes from their cholesterol-lowering effect and also from their anti-inflammatory properties resulting in reduction of oxidative stress [26, 32, 38]. Statins reduce plaque lipid-rich core, macrophage, and foam cell formation, decrease platelet reactivity and promote fibrous cap thickening, leading to reduction in downstream microembolization and thrombotic events [26]. In a recent study from Denmark, 33,552 patients with non-obstructive CAD from a large registry were evaluated using cardiac computed tomography; investigators found that statins were associated with improvement in rates of mortality or MI, with the benefit being proportional to the burden of coronary artery disease [39]. These findings are to be confirmed by the ongoing *W*omen's Ischemi*A* Trial to *R*educe Events in Non-Obst*R*uct*I*ve C*OR*onary Artery Disease (WARRIOR), which is designed to assess the benefit of statins and ACEIs/angiotensin receptor blocker (ARB) medical therapy as well as additional interventions on MACE in symptomatic women with INOCA, as discussed in a separate section [40].

4.2 Non-Conventional Therapies

Studies have shown modest benefit from some of the non-conventional anti-anginal therapies [41–46]. Exercise training modulates adrenergic and nitric oxide pathways, potentially contributing to improvement in coronary flow in CMD [41]. However, clinical trials proving the benefits of exercise are challenging because of issues with patient compliance and cost. Tricyclic antidepressant medications, including imipramine, block multiple receptors, including muscarinic acetylcholine receptors, potentially preventing excessive constriction to acetylcholine, and they inhibit serotonin and norepinephrine reuptake. In a randomized trial of 60 patients with INOCA, imipramine improved symptoms of angina, possibly by its analgesic effects on viscera; however, it did not affect quality of life [42, 43]. Spinal cord stimulation has been associated with improvement in angina

Table 2 Summary of major therapies studied in coronary microvascular dysfunction (CMD) with supporting evidence

Therapy	Major studies, number (*n*) of patients	Supporting evidence
Calcium channel blockers	CorMicA trial, $n = 151$ 16% had vasospastic angina in the intervention group ($N = 75$)	CorMicA trial, for vasospastic angina, calcium channel blockers were associated with improved angina scores (SAQ) at 6 months and 1 year [27, 47] In another study of 16 pts (7 women), angiographically "normal" coronary arteries, IV diltiazem failed to improve CFR in those with reduced CFR [28]
Nitrates	CorMicA trial, $n = 151$ 16% had vasospastic angina in the intervention group ($N = 75$)	CorMicA trial, for vasospastic angina, nitrates were associated with improved angina scores (SAQ) at 6 months and 1 year [27, 47]
Beta-blockers	CorMicA trial, $n = 151$, 57.3% had microvascular angina in the intervention group ($N = 75$)	CorMicA trial, tailored treatment for microvascular dysfunction with beta blocker (nebivolol) associated with improved angina scores (SAQ) at 6 months and 1 year [27, 47] In another study of 18 pts, Doppler-flow wire derived core blood flow velocity measurements 10 controls and 8 pts with CAD, IV nebivolol increased CFR in both controls and CAD patients [33]
Ranolazine	Randomized cross-over trial, $n = 128$, 96% women	Ranolazine is controversial; in patients with CMD confirmed using invasive coronary reactivity testing or MPRI showed no differences in symptoms or MPRI. However, in a sub analysis based on baseline CFR by invasive testing, ranolazine showed benefit in patients with reduced CFR at baseline [34, 35]
ACEI/ARB	CorMicA trial, 151 patients, 57.3% had microvascular angina in the intervention group ($N = 75$)	CorMicA trial, tailored treatment for microvascular dysfunction with ACEI was associated with improved angina scores (SAQ) at 6 months and 1 year [27, 47] Sub-study NIH Women Ischemia Syndrome Evaluation (WISE) of 78 women with INOCA and CFR < 3.0, 61 women completed study- ACEI (quinapril 80 mg/day) improved CFR at 16 weeks. Both ACEI and CFR increase contributed to symptom improvement [36]
Statins	CorMicA trial, $n = 15$, 57.3% had microvascular angina in the intervention group ($N = 75$) Danish registry including 33,552 patients	CorMicA trial, tailored treatment for microvascular dysfunction with statins was associated with improved angina scores on SAQ over 6 months and 1 year [27, 47] Cardiac CTA; statins were associated with improved mortality & MI, benefit being proportional to burden of CAD [38]
Physical training/exercise	Randomized study, $n = 26$	Physical training associated with increased ex capacity and less angina [41]
Tricyclic antidepressants	Randomized study, $n = 60$	Imipramine improved angina, possibly by visceral analgesic effect [42, 43]
Spinal cord stimulation	Study of 7 patients with refractory angina and normal coronaries	Spinal cord stimulation associated improved angina and exercise tolerance [44]
L-Arginine	Randomized study, $n = 26$	L-Arginine improved angina and vascular function but associated with increased MI in obstructive CAD [45]
Low-dose hormonal therapy	Randomized study, post-menopausal women from WISE, $n = 35$	HRT associated with improved chest pain and menopausal symptoms, but not ischemia or brachial artery endothelial function. [46]

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CFR* coronary flow reserve, *CMD* coronary microvascular dysfunction, *CTA* computed tomography angiography, *FFR* fractional flow reserve, *HRT* hormone replacement therapy, *IMR* index of microcirculatory resistance, *INOCA* ischemia with non-obstructive coronary arteries, *IV* intravascular, *MI* myocardial infarction, *MPRI* myocardial perfusion reserve index, *SAQ* Seattle Angina Questionnaire

and exercise tolerance [44]. Similarly, L-arginine seems to improve angina and vascular function but was associated with increased risk of myocardial infarction in patients with obstructive CAD [45]. In a study of post-menopausal women from WISE, low-dose hormonal therapy improved chest pain symptoms, menopausal symptoms, and quality of life, but was not associated with improved ischemia or endothelial dysfunction [46].

5 The CorMicA Trial

With the knowledge gaps regarding the prevalence, optimal diagnostic approach, and management of patients with CMD, the CorMicA trial was performed to answer some of these questions. Indeed, we learned from the CorMicA trial that non-obstructive CAD was more prevalent that we initially thought (compromising 39% of all patients with symptoms of myocardial ischemia), and that stratified medical therapy based on the type of CMD led to improvement in symptoms and outcomes [27]. The CorMicA classified 151 patients with suspected CMD into the following types: microvascular angina, vasospastic angina, or neither, based on their invasive coronary assessment [27]. Briefly, invasive coronary testing involved passing a pressure wire via a guiding catheter (typically into the left anterior descending coronary artery) for assessment of coronary flow reserve (abnormal < 2.0), the index of microcirculatory resistance (abnormal ≥ 25), and fractional flow reserve (abnormal ≤ 0.80) during intravenous infusion of adenosine (140 µg/kg/min). Incremental concentrations of acetylcholine (10^{-6}, 10^{-5}, 10^{-4} mol/L) were then sequentially infused during 2-min periods, followed by vasospasm provocation testing (acetylcholine bolus, 100 µg for left coronary system or 50 µg for right coronary artery), and finally 300 µg of glyceryl trinitrate. While vasospastic angina was defined as epicardial vasoconstriction $\geq 90\%$ in response to acetylcholine with reproduction of the usual chest pain and ischemic electrocardiographic changes, microvascular angina was defined based on the standardized Coronary Vasomotion Disorders International Study Group (COVADIS) as symptoms of myocardial ischemia, non-obstructive CAD, and evidence of microvascular dysfunction by abnormal microvascular resistance, coronary flow reserve or microvascular spasm.

A total of 151 patients were randomized; patients in the intervention group ($N = 75$ patients) were assigned to specific management strategy based on their type, while patients in the control group ($N = 76$ patients) received the concurrent standard of care. Of the intervention group, 57.3% had microvascular angina, compared with 46.1% in the control group. On the other hand, 16% of the intervention group and 17.1% of the control group had vasospastic angina. Mixed microvascular angina and vasospastic angina was present in 18.7% in the intervention group and 22.4% in the control group. Neither endotype was found in 8% in the intervention group and 14.5% in the control group [27, 47]. In the intervention group, patients with vasospastic angina were prescribed calcium channel blockers and/or nitrates, while patients with microvascular angina were prescribed beta-blockers with consideration of ACEIs and statins. Patients with neither type were deemed patients with non-cardiac chest pain, and were discharged from cardiology clinic and anti-anginal medications were discontinued (Fig. 2). The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% CI 5.0–18.4; $p = 0.001$). In addition, the intervention led to improvements in the mean quality-of-life score (EQ-5D index 0.10 U; 95% CI 0.01–0.18; $p = 0.02$) and visual analogue score (14.5 U; 95% CI 7.8–21.3; $p < 0.001$). There were no differences in MACE (composite of all-cause mortality, myocardial infarction, unstable angina hospitalization or revascularization, heart failure hospitalization, and cerebrovascular event) at the 6-month follow-up (2.6% controls vs 2.6% intervention; $p = 1.00$) [27]. Similarly, at 1-year follow-up, 142 patients completed the Seattle Angina Questionnaire assessment and overall angina (Seattle Angina Questionnaire summary score) improved in the intervention group by 27% (difference 13.6 units; 95% CI 7.3–19.9; $p < 0.001$). Quality of life (EQ-5D index) improved in the intervention group relative to the control group (mean difference 0.11 units [18%]; 95% CI 0.03–0.19; $p = 0.01$). After a median follow-up duration of 19 months, occurrence of a MACE was similar between the groups, occurring in 9 subjects (12%) in the intervention group and 8 (11%) in the control group ($p = 0.80$) [47]. Using this strategy, physicians were more likely to prescribe anti-anginal medications in the intervention group. Similarly, patients were more likely to take calcium channel blockers at 6 months in the intervention group. The CorMicA trial showed that stratified therapy based on the type of microvascular dysfunction led to improvement in angina and quality of life. Patients with coronary vasospasm showed benefit from vasodilator therapy with calcium channel blockers and/or nitrate therapy, while patients with microvascular angina experienced improvement in their symptoms with beta-blockers and consideration of ACEI/statin therapy [27, 47].

6 Knowledge Gaps and Ongoing Trials

While CorMicA showed evidence supporting the benefit of an algorithmic approach to patients with suspected CMD with stratified treatment based on the specific endotype of CMD, CMD remains a heterogenous clinical condition

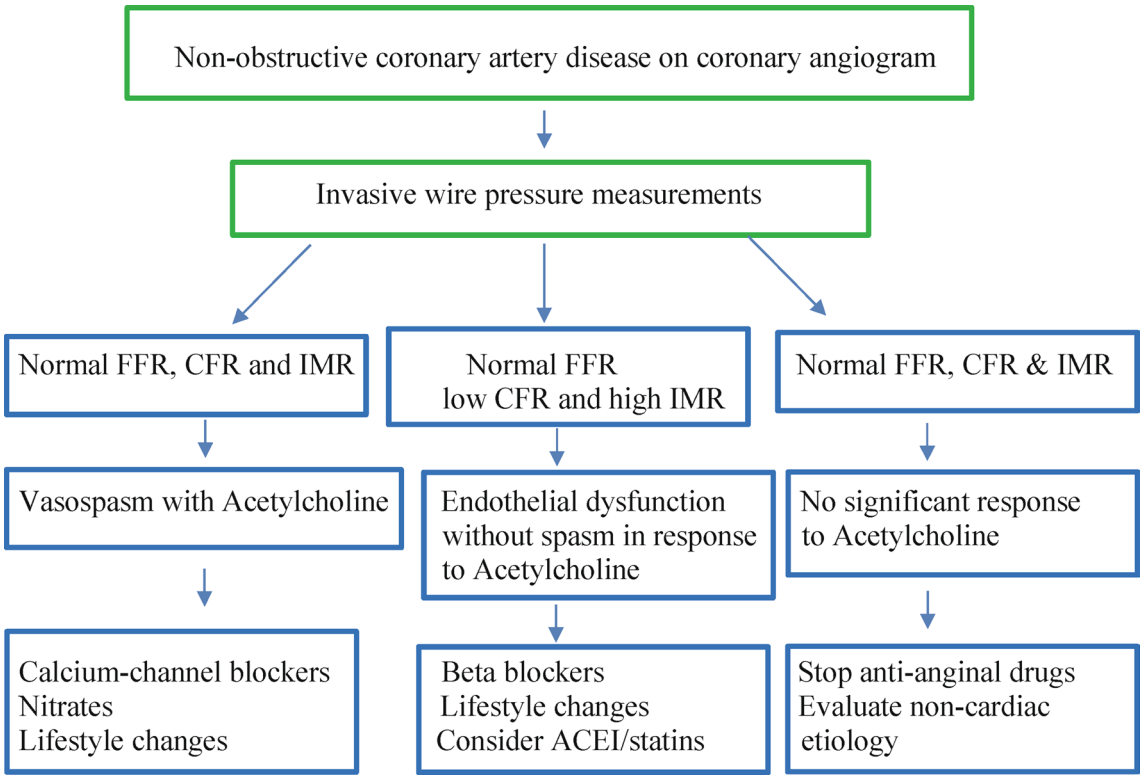

Fig. 2 Summary of diagnosis and treatment of coronary microvascular dysfunction (CMD) based on the CorMicA trial. *ACEI* angiotensin-converting enzyme inhibitor, *CFR* coronary flow reserve, *FFR* fractional flow reserve, *IMR* index of microcirculatory resistance

with knowledge gaps in understanding the pathophysiology, potential disease mechanisms, interactions of different risk factors, and optimal management options with their impact on outcomes as well as prognosis of different types of CMD [27, 47]. Studies have shown that INOCA is associated with higher risk of developing HFpEF, through potential mechanisms including aortic stiffness and ventricular remodeling. However, this association is not completely understood and future studies addressing this knowledge gap are needed [22, 23]. Observational studies have shown potential benefit of ACEIs and statins, as well as beta-blockers; however, the benefit of these medications compared to no medication has not been confirmed in large randomized clinical trials [26, 28, 32, 35–37]. Thus, large randomized clinical trials are needed to confirm the benefit and role of the different pharmacological and behavioral treatments. There are a few ongoing trials in this arena to address the optimal therapy in patients with CMD. The WARRIOR (ClinicalTrials.gov NCT03417388) is a multicenter, randomized, blinded outcome trial to evaluate the benefit of statin and ACEI/ARB therapy on MACE in symptomatic women with INOCA [40]. The Precision Medicine With Zibotentan in Microvascular Angina (PRIZE) (ClinicalTrials.gov NCT04097314) is another trial assessing the benefit of zibotentan, an oral endothelin A receptor antagonist, in patients with microvascular dysfunction [48]. The CorCTCA (ClinicalTrials.gov NCT 03477890) is an ongoing trial aiming to clarify the prevalence and outcomes of INOCA when standard care is based on coronary computed tomography angiography [49].

6.1 The WARRIOR Trial

Given the scarcity of strong evidence evaluating the optimal therapy in women with signs and/or symptoms of suspected ischemia and non-obstructive CAD, as our current data are mainly based on observational studies with the exception of CorMicA trial, the WARRIOR trial was designed to assess the benefit of intensive medical therapy with high intensity statin and ACEIs or angiotensin receptor blocker therapy versus the usual care in a multicenter prospective randomized blinded outcome study (Fig. 3) [40]. In addition to the former statins and ACEIs/ARB therapy, women will receive aspirin if there is no contraindication or high bleeding risk, behavioral lifestyle assessment and counseling with weight loss, exercise, and smoking cessation, as well as quality-of-life questionnaires. The hypothesis of this trial is that the intensified medical therapy will reduce MACE compared with the usual care. The primary

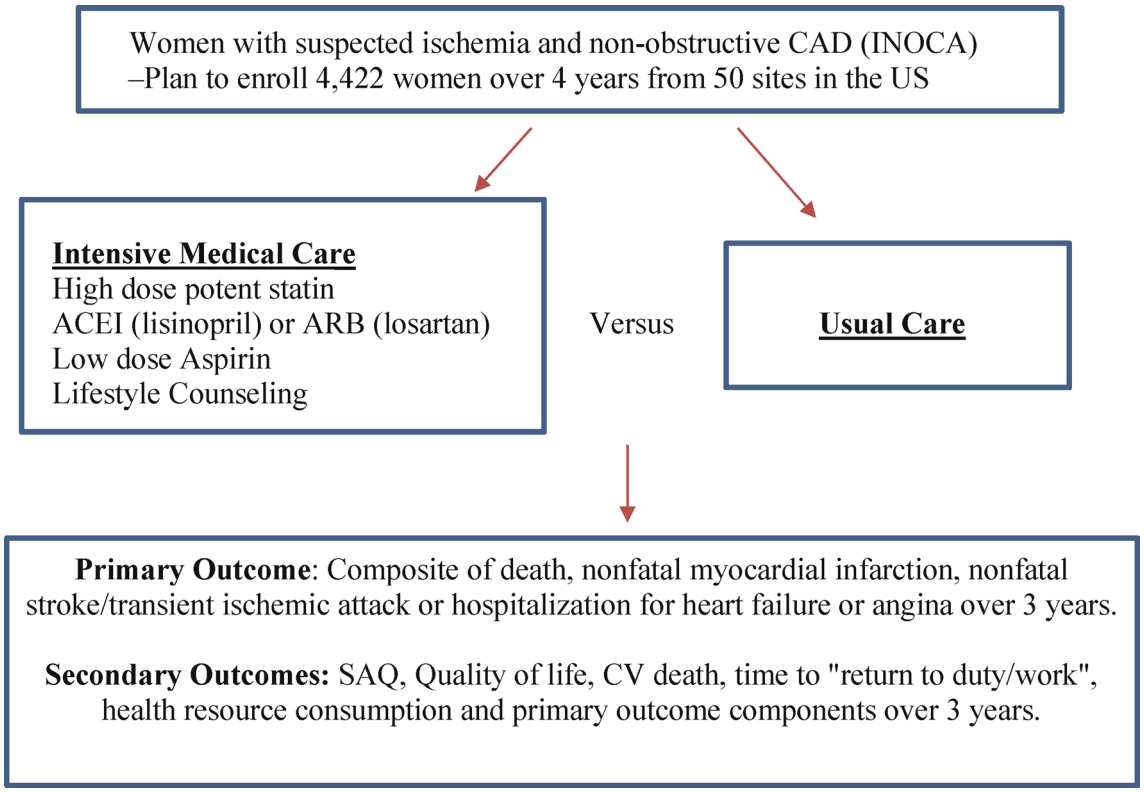

Fig. 3 Summary of the WARRIOR trial design. *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CV* cardiovascular, *INOCA* ischemia with non-obstructive coronary arteries, *SAQ* Seattle Angina Questionnaire, *US* United States

outcome is the composite of death, nonfatal myocardial infarction, nonfatal stroke/transient ischemic attack, or hospitalization for heart failure or angina. Secondary outcomes include quality of life, cardiovascular death, angina, time to "return to duty/work", health resource consumption, and primary outcome components. Enrollment was started in 2018 and the estimated completion time is December 2022, with 4422 enrolled over 4 years from 50 sites in the USA. The study will evaluate the benefits of these medications and interventions in patients with INOCA and could potentially contribute to practice-changing recommendations by providing strong scientific evidence confirming the benefit of these medications in INOCA patients and potentially implementing guideline recommendations regarding the management of these patients [40].

7 Summary and Conclusions

Coronary microvascular dysfunction has been increasingly recognized as a heterogenous clinical entity with different subtypes and response to treatment. Knowledge of the diagnostic evaluation, including invasive assessment, is key to diagnose these clinical entities. Importantly, medical stratification based on the type of condition has shown benefit in improving angina in these patients. The WARRIOR trial is a promising landmark trial, which is currently enrolling patients and will address some of the unanswered questions for management of women with INOCA. Nevertheless, it is important to understand that there are many other knowledge gaps in this field and randomized clinical trials are needed to help us address some of these.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest Unrelated to this manuscript content, Dr. Elgendy has received research grants from Caladrius Biosciences, Inc. Drs Ya'Qoub, Chen and Pepine declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Availability of data and material Not applicable

Code availability Not applicable

Author contributions IYE performed the literature search, reviewed the data, wrote and edited the manuscript. LY performed the literature search, reviewed the data, wrote and edited the manuscript. KHC performed the literature search and wrote part of the manuscript. CJP reviewed the data and edited the manuscript.

References

1. Virani S, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report from the American Heart Association. Circulation. 2021;143(8):e254–743.
2. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA. 2014;312:1754–63.
3. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, ACC CVD in Women Committee, et al. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol. 2015;66:1918–33.
4. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2011;33(6):734–44.
5. Ya'qoub L, Elgendy IY, Pepine CJ. Syndrome of nonobstructive coronary artery diseases: a comprehensive overview of open artery ischemia. Am J Med. 2021. https://doi.org/10.1016/j.amjmed.2021.06.038.
6. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, WISE Investigators, et al. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study, part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006;47(suppl):S4–20.
7. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, WISE Investigators, et al. 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):S21–9.
8. Patel MR, Dai D, Hernandez AF, Douglas PS, Messenger J, Garratt KN, et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. Am Heart J. 2014;167(6):846-52.e2.
9. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, et al. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. Circulation. 2015;131:1054–60.
10. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. EuroIntervention. 2021;16(13):1049–69.
11. Pepine CJ. Multiple causes for ischemia without obstructive coronary artery disease: not a short list. Circulation. 2015;131:1044–6.
12. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356:830–40.
13. Mejia-Renteria H, van der Hoeven N, van de Hoef TP, Heemelaar J, Ryan N, Lerman A, et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. Int J Cardiovasc Imaging. 2017;33:1041–59.
14. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AH, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. Eur Heart J. 2020;41(37):3504–20.
15. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, et al. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). J Interv Cardiol. 2010;23:511–9.
16. 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;52:1369–77.
17. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55:2825–32.
18. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. Nat Rev Cardiol. 2015;12:48–62.
19. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, et al. 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(4):e002481. https://doi.org/10.1161/CIRCIMAGING.114.002481.
20. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, NHLBI Women's Ischemia Syndrome Evaluation (WISE), et al. 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.
21. 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;6:660–7.
22. Del Buono MG, Montone RA, Camilli M, Carbone S, Narula J, Lavie CJ, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;78(13):1352–71.
23. Elgendy IY, Pepine CJ. Heart failure with preserved ejection fraction: Is ischemia due to coronary microvascular dysfunction a mechanistic factor? Am J Med. 2019;132(6):692–7.
24. Pepine CJ, Petersen JW, Bairey Merz CN. A microvascular-myocardial diastolic dysfunction state and risk for mental stress ischemia: a revised concept of ischemia during daily life. JACC Cardiovasc Imaging. 2014;7(4):362–5.
25. Reynolds HR, Picard MH, Spertus JA, Peteiro J, Lopez-Sendon JL, Senior R, et al. Natural history of patients with ischemia and no obstructive coronary artery disease: the CIAO-ISCHEMIA Study. Circulation. 2021;144(13):1008–23.

26. Bairey Merz CN, Pepine CJ, Shimokawa H, Berry C. Treatment of coronary microvascular dysfunction. Cardiovasc Res. 2020;116(4):856–70.
27. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA Trial. J Am Coll Cardiol. 2018;72(23 Pt A):2841–55.
28. 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(2):135–43.
29. 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;56:242–6.
30. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. Am J Cardiol. 1999;84:854–6.
31. Ozçelik F, Altun A, Ozbay G. Antianginal and anti-ischemic effects of nisoldipine and ramipril in patients with syndrome X. Clin Cardiol. 1999;22:361–5.
32. Zhang X, Li Q, Zhao J, Li X, Sun X, Yang H, et al. Effects of combination of statin and calcium channel blocker in patients with cardiac syndrome X. Coron Artery Dis. 2014;25:40–4.
33. Togni M, Vigorito F, Windecker S, Abrecht L, Wenaweser P, Cook S, et al. Does the beta-blocker nebivolol increase coronary flow reserve? Cardiovasc Drugs Ther. 2007;21(2):99–108.
34. Bairey Merz CN, Handberg EM, Shufelt CL, Mehta PK, Minissian MB, Wei J, et al. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. Eur Heart J. 2016;37:1504–13.
35. Rambarat CA, Elgendy IY, Handberg EM, Bairey Merz CN, Wei J, Minissian MB, et al. Late sodium channel blockade improves angina and myocardial perfusion in patients with severe coronary microvascular dysfunction: Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction ancillary study. Int J Cardiol. 2019;276:8–13.
36. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, et al. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2011;162:678–84.
37. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. Am J Cardiol. 2002;90:974–82.
38. Pizzi C, Manfrini O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac syndrome X: role of superoxide dismutase activity. Circulation. 2004;109:53–8.
39. Øvrehus KA, Diederichsen A, Grove EL, Steffensen FH, Mortensen MB, Jensen JM, et al. Reduction of myocardial infarction and all-cause mortality associated to statins in patients without obstructive CAD. JACC Cardiovasc Imaging. 2021. https://doi.org/10.1016/j.jcmg.2021.05.022.
40. Handberg EM, Merz CNB, Cooper-Dehoff RM, Wei J, Conlon M, Lo MC, et al. Rationale and design of the Women's Ischemia Trial to Reduce Events in Nonobstructive CAD (WARRIOR) trial. Am Heart J. 2021;237:90–103.
41. Eriksson BE, Tyni-Lennè R, Svedenhag J, Hallin R, Jensen-Urstad K, Jensen-Urstad M, et al. Physical training in syndrome X: physical training counteracts deconditioning and pain in syndrome X. J Am Coll Cardiol. 2000;36:1619–25.
42. Cannon RO, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, et al. Imipramine in patients with chest pain despite normal coronary angiograms. N Engl J Med. 1994;330:1411–7.
43. 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;19:250–4.
44. Lanza GA, Sestito A, Sandric S, Cioni B, Tamburrini G, Barollo A, et al. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. Ital Heart J. 2001;2:25–30.
45. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. Circulation. 1998;97:2123–8.
46. Merz CN, Olson MB, McClure C, Yang YC, Symons J, Sopko G, et al. Am Heart J. 2010;159:987-e981–7.
47. Ford TJ, Stanley B, Sidik N, Good R, Rocchiccioli P, McEntegart M, et al. 1-year outcomes of angina management guided by invasive coronary function testing (CorMicA). JACC Cardiovasc Interv. 2020;13(1):33–45.
48. Morrow AJ, Ford TJ, Mangion K, Kotecha T, Rakhit R, Galasko G, et al. Rationale and design of the Medical Research Council's Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial. Am Heart J. 2020;229:70–80.
49. Sidik NP, McEntegart M, Roditi G, Ford TJ, McDermott M, Morrow A, et al. Rationale and design of the British Heart Foundation (BHF) Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study. Am Heart J. 2020;221:48–59.