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Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-based Therapies and Research Agenda for the Next Decade

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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, European Society of Cardiology), convened a working group to develop a consensus on the syndrome of myocardial ischemia with no obstructive coronary arteries (INOCA). In general, these patients have elevated risk for a cardiovascular event (including acute coronary syndrome, heart failure hospitalization, stroke, and repeated cardiovascular procedures) vs reference subjects, and appear to be at higher risk for development of heart failure with preserved ejection fraction (HFpEF). A subgroup of these patients also has coronary microvascular dysfunction (CMD) and evidence of inflammation. This document provides a summary of findings and recommendations toward the development of an integrated approach for identifying and managing patients with INOCA, and outlining 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-

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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.

Keywords

Ischemia with no obstructed coronary arteries (INOCA); coronary microvascular dysfunction (CMD)

Definition and Terminology

Patients presenting with the syndrome of symptoms and signs suggesting ischemic heart disease (IHD) 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), i.e. ≥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. While there is likely overlap between INOCA and *myocardial infarction 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 provide next steps for developing evidence-based management strategies for INOCA, a “Think Tank” was convened at the American College of Cardiology (ACC) Heart House, Washington D.C., May 17, 2016. This report summarizes those presentations and discussions.

Prevalence, Costs and Prognostic Significance

The ACC-National Cardiovascular Data Registry (ACC-NCDR) and National Heart, Lung and Blood Institute–sponsored Women’s Ischemic Syndrome Evaluation (WISE) databases suggest that at least 3–4 million women and men with signs/symptoms suggestive of myocardial ischemia have no obstructive CAD.[8, 9] Such individuals incur health-care costs and disabilities similar to many with obstructive CAD, in part due to angina and heart failure (HF) hospitalizations and repeated testing.[8, 10] These cost burdens related to hospitalizations and repeated 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 from CVD, predominantly IHD[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 IHD 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, non-fatal myocardial infarction [MI], non-fatal stroke, and HF hospitalization) rate exceeding 2.5%

yearly by 5 years, as well as elevated rates of readmission, 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 non-obstructive 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).

Predictors of Adverse Outcomes

Older age, hypertension, diabetes, and smoking have been associated with increased mortality, while sex, hyperlipidemia, family history of premature CAD, or pre-test CAD likelihood have not.[19] Risk-adjusted analyses found that "*non-obstructive*" CAD conferred increased mortality risk vs. that of patients with "no evident" CAD.[19]

Chest pain persisting at 1-year follow-up predicted MACE among those with INOCA in the WISE.[20] Measures of non-obstructive CAD extent and severity (e.g., 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 (CCTA), with patients propensity-matched for age, CAD risk factors, and "angina typicality", observed elevated death/MI rates in those with "non-obstructive CAD" vs "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 (e.g. myocarditis, etc.), 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 will focus on clinical situations where the pathophysiologic 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 (Kv 1.5) are critical in coupling myocardial blood flow to myocardial metabolism. Table 1 summarizes intrinsic mechanisms of coronary blood flow regulation.

Coronary Microvascular Dysfunction (CMD)

One proposed mechanism contributing to INOCA is CMD[24], defined as epicardial and/or microvascular endothelial and/or non-endothelial 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, 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 non-obstructive atherosclerosis”, to those with “normal appearing angiograms”, to those with only coronary microvacular 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 for diagnosis of 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 INOCA women, with a 5-year MACE rate of 27%, vs. 9.3% for those with a CFR ≥2.32 (p=0.01).[30] Importantly, CFR was a continuous predictor of MACE, similar to blood pressure and LDL-C, rather than having a step-like threshold for “normal vs 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 ml/min/gm myocardium) by positron emission tomography (PET).[26, 31, 32] The latter study provides the most definitive data on CMD and adverse outcome risk among INOCA patients.[32] In those with CFR_{PET} <2.0, the MACE (cardiac death, MI, late-revascularization, or HF-hospitalization) rate was increased at 3 years vs 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 vs 3.3% and 1.7%, respectively, for those with CFR ≥2.0.[32] Interestingly, while women comprise ~70% of the INOCA population[41], increased risk associated with limited CFR does not appear different for women vs. men (Figure 1). A recent publication demonstrates the excess cardiovascular risk in women relative to men is associated with severely impaired coronary flow reserve, 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 like 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[47] as chronic hyperglycemia reduces endothelial-dependent and -independent coronary vasodilator capacity.[48, 49] Hypercholesterolemia may lead to CMD[50], but higher HDL-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 like those associated with inflammation may contribute.[51, 52] There is a correlation between high sensitivity C-reactive protein (hsCRP) and number of ischemic episodes during ambulatory ECG monitoring.[53] CRP is increased among subjects with microvascular angina vs. controls, further supporting a possible role of inflammation and endothelial dysfunction in causing CMD.[54] Patients with increased hsCRP have an attenuated rise in CBF in response to acetylcholine (Ach).[55, 56] Systemic lupus erythematosus is frequently associated with angina and CMD,[57] while 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 (aPWV) with other vessel stiffness indices explained >50% of CFR variance in a WISE substudy.[60] Arterial stiffness is known to predict cardiovascular events beyond traditional risk factors. When arterial stiffness indices were assessed by magnetic resonance imaging (MRI), ultrasound, and tonometry in asymptomatic subjects from the community,[61] peripheral and central pulse pressure, augmentation index, carotid-femoral PWV, and aortic arch PWV 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 PWV after age 50.[61]

Atherosclerosis

The pathophysiology of atherosclerosis has shifted from a lipid storage disease with large lipid pool thin fibrous cap atheroma (e.g. “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, LDL-cholesterol, environmental factors such as tobacco, etc.) activates endothelial cells 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, chemo-attractant 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 organ(s) involved.[62] Evidence linking microvascular and inflammatory responses to risk factors indicates that oxidative stress, reduced nitric-oxide (NO)-bioavailability, and endothelial activation are common early features of coronary microvascular responses to atherosclerosis risk factors.[63]

Almost all INOCA patients 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 non-obstructive CAD.[64] Plaque rupture by IVUS was not observed in INOCA patients from two series of patients with chronic angina. [5, 22, 64] Two single-center reports of non-obstructive 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 plaque ruptures frequently appeared in more voluminous plaques with large plaque burden and positive remodeling.[5]

Non-Obstructive CAD

Prior work evaluating patients suspected to have myocardial ischemia found ~40% of women and 8% of men had "non-significant CAD" (30%–49% stenosis).[14] The Coronary Artery Surgery Study (CASS) registry reported 39% of women and 11% of men with angina had "normal coronary arteries."[65] However, CASS lacked an angiographic core lab, and in a sample 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 non-obstructive CAD with increased risk for adverse outcomes. These include number of major vessels involved with non-obstructive CAD,[3] WISE-CAD Severity Score,[17] and TIMI-frame counts.[68] In a European consecutive case registry of patients undergoing clinically-indicated coronary angiography, the prevalence of non-obstructive CAD was 65% among women and 32% in men.[2] The ACC-NCDR prospective registry of patients undergoing clinically indicated invasive coronary angiography found that the prevalence of non-obstructive CAD was 51% in women and 32% in men.[9] Diffuse non-obstructive CAD is increasingly recognized with the more widespread use of FFR which may be of use to assess long moderate lesions. Measures from CCTA 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 auto regulatory capacity, allowing transmission of increased blood pressure to the microvessels.[24] Along with hydraulic factors

like 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 (TG) content (0.83 ± 0.12% vs. 0.43 ± 0.06%; P = 0.025) and lower diastolic circumferential strain rate (168 ± 12 vs. 217 ± 15%/s; P = 0.012), with myocardial TG 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. Mitochondria functions including ROS signaling, apoptosis, steroid synthesis, hormonal signaling (mtER), and sexual dimorphism in the expression of mitochondria-related genes may be involved.[71]

Obesity, Metabolic Syndrome and Diabetes

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 > men).[4, 73] Coronary microvascular abnormalities are highly prevalent and worsen with progressive glucose intolerance with or without obstructive CAD, and non-obstructive CAD is highly prevalent in those with diabetes.[34, 74, 75]

Cardiac Autonomic Nervous System (ANS)

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

An abnormal vascular response to Ach 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 α1-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/adenosine diphosphate (ADP) stimulation, decreases after exercise in patients with angina, positive exercise tests, and "smooth coronary arteries" (e.g. INOCA).[85] Flow cytometry measures at rest and exercise[86] in INOCA patients demonstrated that increases in platelet receptor expression and leukocyte–platelet aggregate formation (to ADP) were consistently lower after exercise than before. These findings agree with and expand upon prior work demonstrating lower whole blood platelet reactivity to collagen/ADP in INOCA patients after exercise, in contrast with absence of change in controls and an increase in CAD patients.[13, 14] Changes in platelet receptor expression and leukocyte-platelet aggregate formation have been reported following exercise in INOCA,[86] and adenosine has been shown to inhibit ADP- and thrombin-induced monocyte-platelet aggregates in INOCA.[87]

Diagnosis

Invasive Testing

Coronary blood flow (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: Ach, bradykinin, substence-P, L-NMMA, shear-stress, and predominantly endothelium-independent probes: adenosine or 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 (CPT), and mental stress have also been used to elicit abnormalities in CBF. WISE-CVD project data suggest a strong correlation between Ach and CPT coronary artery diameter changes in women.[22] Reports from testing over 1500 patients indicate an excellent safety record with no deaths and <1% procedure-related adverse experiences like those observed with coronary angiography.[88–90]

Noninvasive Testing

Position Emission Tomography (PET)—PET is a highly accurate, reproducible and modifiable procedure providing comprehensive evaluation of CBF, including perfusion, LV function, and CFR. There is a strong association between impaired CFR and impaired LV myocardial relaxation or elevated filling pressures; 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 (HR, 1.06), LVEF (10% increase, HR, 0.56), CFR (HR, 0.80 for each 10% increase).

Transthoracic Echo-Doppler—In another study of patients with chest pain without obstructive CAD and coronary flow velocity (CFV), by pulsed wave Doppler of the LAD at

rest and after dipyridamole, 26% had CFV reserve <2.0.[92] Those with low CFV reserve had significantly greater physical limitation and disease perception scores using the Seattle Angina Questionnaire.

Cardiac Magnetic Resonance Imaging (cMRI)—Failure of subendocardial perfusion to increase appropriately in response to stress can be detected by cMRI among INOCA subjects.[93, 94] A semi-quantitative approach with measurement of myocardial perfusion reserve index (MPRI) detects CMD in women with INOCA.[95] Those with CMD, by abnormal invasive CRT, had reduced MPRI vs normal women. Because the methodology uses standard equipment and protocol available in tertiary hospitals without radiation, MPRI appears useful for diagnosis and management of INOCA and deserves additional evaluation.

Management

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

Statins, ACE-Inhibitors (ACE-I), and aspirin (ASA)

Multiple prior statin trials using IVUS have documented prevention of progression, or even regression, of atherosclerosis in coronary arteries, as well as coronary endothelial and/or vascular smooth muscle function in subjects with non-obstructive CAD.[96, 97] Statins not only lower cholesterol, but also have anti-atherosclerotic 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 administration of atorvastatin improved CFR after 2 months[100] and 6 months.[101] Angiotensin converting enzyme (ACE) inhibitors have been shown to improve exercise tolerance and angina symptoms.[102] In the WISE control trial, women who received quinapril had improved CFR after 16 weeks compared to the placebo group. In addition, the experimental group also had improvement in angina symptoms based on 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 inhibitor, the addition of an aldosterone blocker did not improve endothelial function.[105] In subjects with diabetes, 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 vs placebo. Mechanistically, the combination produced greater increases in brachial artery flow-mediated dilation vs placebo and reduced extracellular superoxide dismutase.[102]

Anti-platelet agents

A majority of patients with CMD have endothelial dysfunction, and while angiography shows no significant plaque burden, IVUS has demonstrated coronary atherosclerosis in

most patients[22, 64]. Therefore, ACC/AHA chronic stable angina guidelines [109] can be extrapolated to use of anti-platelet agents such as aspirin in patients with evidence of ischemia and no obstructive CAD.

Anti-anginal agents

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

Management of risk factors includes control of diabetes 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, fruits and vegetables consumption and regular physical activity.[116–118]

Few studies addressed the use of beta-blockers. The existing studies included patients with signs and symptoms of ischemia, but without definitive diagnosis of CMD. Beta-blockers reduce myocardial oxygen consumption and increase diastolic filling time. Atenolol has been shown to reduce number of angina episodes[119] and also 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 have improved symptoms, less nitrate usage, and improved exercise tolerance after being treated with verapamil or nifedipine.[123]

Nitrates achieve anti-anginal effect through venodilation to reduce preload; in addition, they may have some coronary vasodilatory effect. The use of nitrates may improve patient's symptoms, but there are limited data on their effect on endothelial 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 on 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 two-week course of ranolazine vs. 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 were 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, reduces smooth muscle cell hypercontraction[131] and is being investigated currently and has potential for CMD. It has been shown to be effective for vasospastic angina. Preliminary studies showed patients pretreated with fasudil did not manifest evidence of ischemia with acetylcholine infusion, compared to saline pretreatment.[132]

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

Given that impaired cardiac nociception may be involved in CMD, tricyclic antidepressants can be considered, as 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 from its significant side effects.

Non-pharmacologic treatments can be effective in controlling patient symptoms. Spinal cord stimulation has been shown to normalize abnormal pain perception[139] and improve angina symptoms and increase exercise tolerance.[140] Enhanced external counterpulsation uses pneumatic cuffs applied to 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 as it improves blood pressure, BMI and exercise capacity.[144]

In summary, small studies support the use of statins and ACE-Is to prevent progression of non-obstructive coronary atherosclerosis, 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:

1. stable, chronic (several weeks or longer) symptoms suggesting IHD, such as chest discomfort, both with classic (e.g. angina pectoris) and atypical features in terms of location, quality, and inciting factors;
2. objective evidence for myocardial ischemia from the ECG and/or a cardiac imaging study (echocardiography, nuclear imaging, MRI or spectroscopy) at rest or during stress (exercise, mental, or pharmacologic);
3. absence of flow-limiting obstruction by coronary angiography (invasive or CTA) as defined by any epicardial coronary artery diameter reduction ≥50% and/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. While recent data suggest that ~5% of clinically stable women with angina and INOCA have epicardial spasm with intracoronary Ach testing, the role of microvascular coronary spasm requires additional study. The potential for INOCA to evolve into an ACS (e.g. MINOCA) and/or HF with preserved ejection fraction (HFpEF) requires additional study from large, prospective cohorts.

Management

Knowledge gaps exist regarding the pathogenesis and management of INOCA. For example, why are certain CV 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 non-obstructive CAD, CFR, MPRI, PET in these patients? How often does INOCA/CMD progress to HFpEF, and if so, 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.

Research Agenda for the Next Decade

The following recommendations address three overarching goals: 1) to formulate phenotypic classification of INOCA patients, based on clinical presentation, pathophysiological mechanisms, and prognosis; 2) to develop diagnostic algorithms based on this classification

system and; 3) to develop management approaches to reduce or prevent symptoms and modify risk for adverse outcomes.

A. Design adequately powered, population-based natural history studies/registries of INOCA patients, 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 detection and quantitation of non-obstructive atherosclerosis using invasive coronary angiography, CCTA 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, HFpEF-hospitalization, MI, cardiac death) in INOCA patients.

B. Develop markers as “risk reporters” among “high-risk INOCA patients” that include clinical and advanced technology variables (e.g., proteomic, gene expression, cell-based, exosomes, miRNAs, etc.). Validate them in clinical settings, develop informatics platforms for prediction modeling that may require monitoring specific biological “signatures” periodically to discern which are perturbed before a clinical event (e.g., angina, HF-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 CT 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 addition of new variables when they become available. It would be used as a “targeted screening tool” for patients deemed 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 pathophysiologic 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 micro-disruption, enhanced thrombus formation, sympathetic nervous system activation, and other potential triggering mechanisms for ACS.

C. 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-I and lifestyle modification. Conduct exploratory trials using novel interventions based on new phenotypic and mechanistic understanding on risk outcomes.

D. Construct evidence-based diagnostic and therapeutic guidelines for INOCA. Develop physician education and fellowship training programs to enhance

understanding of this syndrome and encourage use of novel risk assessment and management strategies. Develop programs to understand and overcome barriers to clinical implementation of these guidelines.

Conclusion

The prevalence of non-obstructive CAD among clinically ordered coronary angiograms conducted for evidence of suspected myocardial ischemia (INOCA) is increasing.[1–4] A subgroup of these patients has coronary microvascular dysfunction (CMD), an elevated risk for a cardiovascular event (including acute coronary syndrome and repeated cardiovascular procedures), and higher risk for the development of heart failure hospitalization. At present, there is no uniform, comprehensive diagnostic strategy or algorithm for risk stratification for these patients; however invasive and noninvasive coronary flow reserve testing can be useful. Although small trials have suggested benefit from ACE inhibitors 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 INOCA patients, including large outcome clinical trials. This summary of our current understanding of INOCA (Figure 4) support the need for a research agenda for the next decade to facilitate development of evidence-based risk assessment tools and effective therapies for this rapidly growing patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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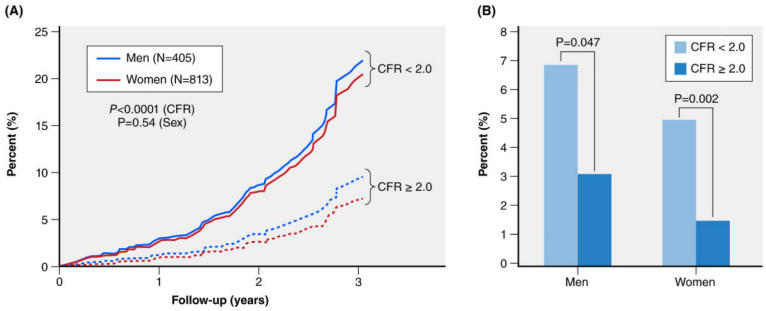

Figure 1.

Sex effects on CMD measured by PET and Adverse Outcomes in Symptomatic Patients without Obstructive CAD. Data obtained from Murthy et al [32]

Figure 2.
Coronary Reactivity Testing Protocol

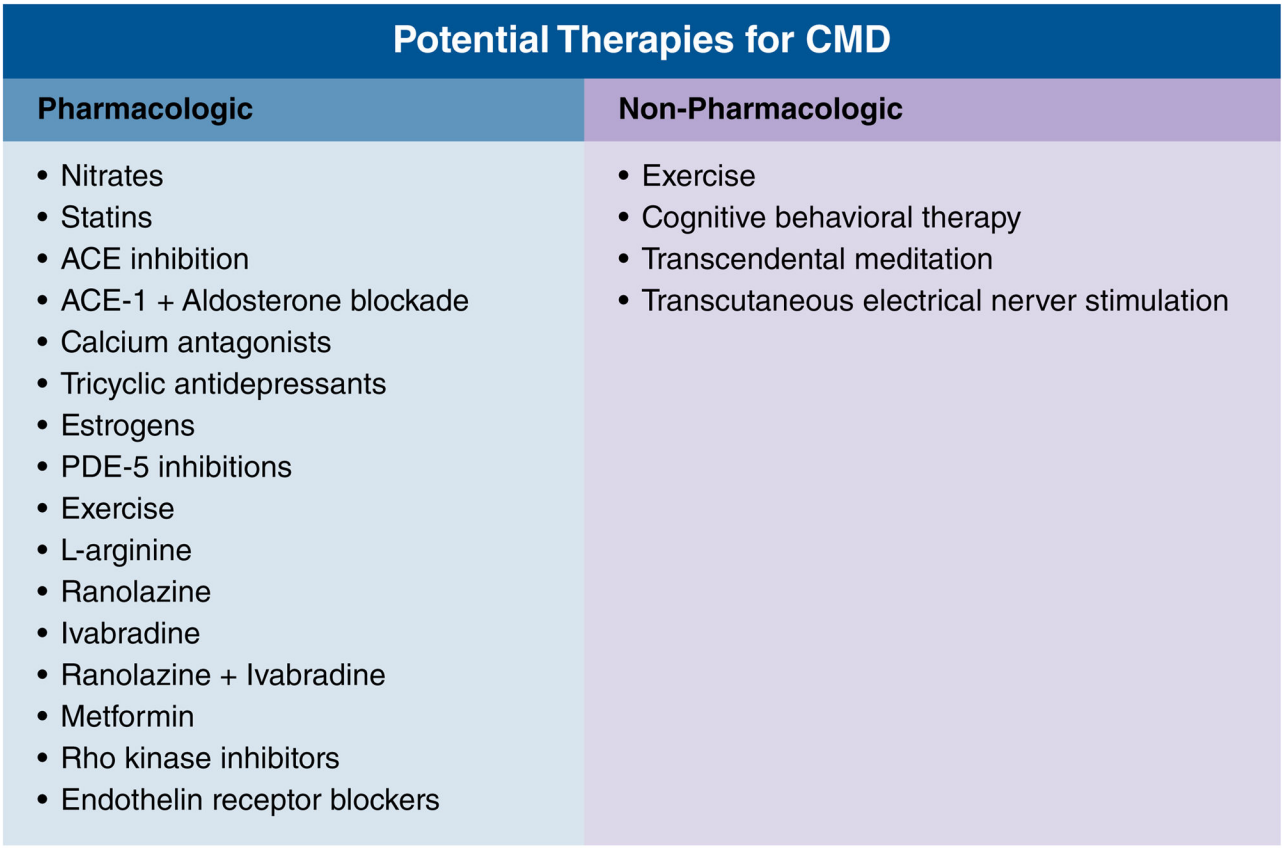

Figure 3.
Potential Therapies for CMD

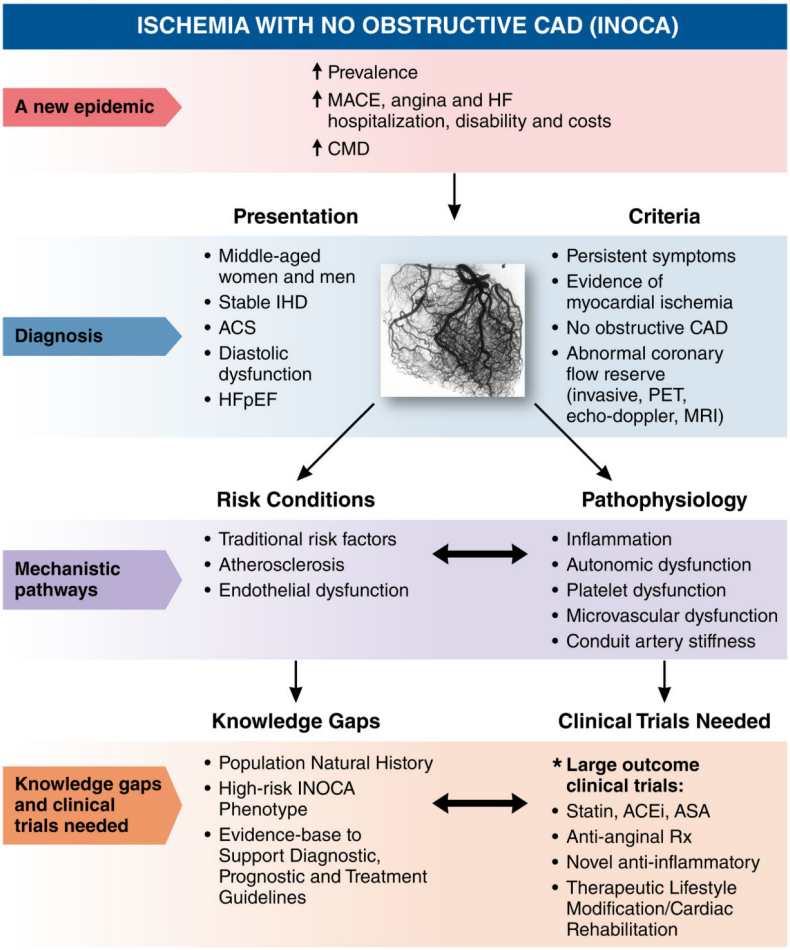

Figure 4.
Ischemia with No Obstructive CAD (INOCA)

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

Table 2

Natural History Studies of Patients with Coronary Microvascular Dysfunction

Author Year	N	Population	Method	Outcome measure	Follow-up	CMD Outcome Predictor	
						Univariate	Multivariate
Pepine (WISE) 2010[30]	189	Women, angina/ischemia most with nonobst CAD	Intracoronary Ado-CFR Doppler flow wire	Death, nonfatal MI, nonfatal stroke, HF hospitalization	5.4 yrs. (mean)	Yes	Yes
Balazs (SZEGED) 2011[31]	45	Women, angina/ischemia, no obstructive CAD	Vasodilator CFR, Doppler /TEE, TTE	Death, CV hospitalization	102±26 mos. 113 median	Yes	Yes
Murthy 2014[32]	1218 813 W 405 M	No obstructive CAD (excluded by CTA or PET)	Stress Perfusion Imaging (PET)	CV death, MI, late revasc. (>90 ds) or HF-hospitalization	3 years	Yes	Yes
Britten 2004[33]	120	Post PCI/mild CAD	IC Papaverine or Ado-CFR Doppler flow wire	Cardiac death, ACS, revasc., stroke	6.5±3 yrs. (14–125 mos.)	Yes	Yes
Schindler 2006[34]	72	CAD risk factors without flow-limiting stenosis	CPT-MBF increase with ^{13}N-NH_3 PET	CV death, ACS, MI, PCI/CABG, stroke, PTA	66±8 mos.	Yes	No
Rigo 2007[35]	86	CAD, LAD 51–75% stenosis	Vasodilator LAD CFR, Doppler /TTE	Non-fatal MI	30 mos. 14 median	Yes	Yes
Nemes 2008[36]	397	Hospitalized, angina, mostly severe CAD, TEE for AA	Vasodilator LAD CFR, Doppler /TEE	CV death, HF. thrombosis	41±12 mos.	Yes	Yes
Herzog 2009[37]	229	Suspect CAD/66% had severe CAD	Vasodilator CFR with ^{13}N-NH_3 PET	CV death, nonfatal MI, hospitalization, PCI/CABG	5.5±2.1 yrs.	Yes	Yes
Tio 2009[38]	344	Severe CAD, not revasc., LV systolic dysfunction	Vasodilator CFR with ^{13}N-NH_3 PET	Cardiac death	85 mos. (1–138 mos)	Yes	Yes
Cortigiani 2010[39]	1,660	Chest pain, Normal DSE	Vasodilator LAD CFR, Doppler /TTE	Death, MI, revasac.	19 mo. median	Yes	Yes
Ziadi 2011[40]	677	Most had severe CAD	Vasodilator CFR with ^{82}Rb PET	CV death, nonfatal MI	387 ds. (375–416 ds)	Yes	Yes

Abbreviations: CAD = coronary artery disease, CFR = coronary flow reserve, CMD = coronary microvascular dysfunction, CV = cardiovascular, DSE = dobutamine stress echo, HF = heart failure, MI = myocardial infarction, PCI = percutaneous coronary intervention, TEE = transesophageal echocardiography.

Table 3

Intra-coronary acetylcholine concentration and infusion

Prepared Concentration	Infusion Rate	Infusion duration	Infused Dose
10^{-6} M (0.182 mcg/mL)	48 ml/hr	3 minutes	0.364 mcg
10^{-4} M (18.2 mcg/mL)	48 ml/hr	3 minutes	36.4 mcg
10^{-4} M (18.2 mcg/mL)	120 ml/hr	3 minutes	108 mcg

Table 4

Definitions of coronary microvascular and macrovascular dysfunction

Coronary Microvascular Dysfunction Pathways	Microvascular Dysfunction	Macrovascular Dysfunction
Non-Endothelial Dependent	CFR in response to adenosine <2.5	Change in coronary artery diameter in response to nitroglycerin <20%
Endothelial 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%	

Abbreviations: CBF = coronary blood flow, CFR = coronary flow reserve, ECG = electrocardiogram

Table 5

Protocol for Invasive Coronary Reactivity Testing

Preparation
Withhold for 48 hours: • Long-acting calcium antagonists *Withhold for 24 hours:* • Caffeine • Long-acting nitrates • Short-acting calcium antagonists • Alpha blockers • Beta blockers • ACE inhibitors/angiotensin receptor blockers/Renin Inhibitors/aldosterone inhibitors *Withhold for 4 hours:* • Sublingual nitroglycerin
Protocol
• Review indications for invasive coronary reactivity testing: – Chest symptoms thought to be angina or equilievent – Evidence of ischemia – Confirmation of no obstructive CAD (stenosis >50%), use FFR if borderline • Assess for increased cardiac sensitivity (e.g., chest pain with contrast infusion or catheter movement) • Record left ventricular end-diastolic pressure (LVEDP) • Administer intravenous heparin (70 units/kg) • Advance Doppler FloWire (0.014-inch) pressure and Flow system (e.g. ComboMap) in to proximal-mid LAD artery • Confirm adequate coronary blood flow velocity signal • Infuse provocative agents (using doses in Figure 2) • Recordings and calculations – 12-lead ECG, and repeated with chest pain or ischemic ECG changes – Average peak blood flow velocity (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 – Coronary blood flow (CBF) = π (coronary artery diameter/2)2 (APV/2) – CBF change = (peak CBF- baseline CBF)/(baseline CBF)

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; ECG = electrocardiogram; FFR = fractional flow reserve; LAD = left anterior descending

Table 6

Treatment of Subjects with Angina, Evidence of Myocardial Ischemia, and No Obstructive CAD Reproduced from [110]

Microvascular Coronary Dysfunction (CMD)
Abnormal Endothelial Function
Angiotensin Converting Enzyme Inhibitors (ACE-I)
HMG CoA Reductase Inhibitors (Statins)
L-arginine supplementation
Aerobic Exercise
Enhanced External Counterpulsation (EECP)
Abnormal Non-Endothelial Function
Beta-blockers/alpha-beta blockers
Nitrates
Anti-Anginal
Ranolazine
Ivabradine
Xanthine derivatives
Abnormal Smooth Muscle Function (Prinzmetal's Angina)
Calcium Channel Blockers
Nitrates
Abnormal Cardiac Nociception
Low Dose Tricyclic Medication
Spinal Cord Stimulation
Cognitive Behavioral Therapy