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Insights to advance our management of myocardial ischemia: *From obstructive epicardial disease to functional coronary alterations*

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ABSTRACT

Study objective: The Coronary Vasomotor Disorders International Study Group (COVADIS) invited leading experts to address strategies to enhance our clinical understanding of INOCA with an emphasis on the management of coronary vasomotor disorders.
Design: Under-recognition of coronary vasomotor disorders, distinguishing different presentations of angina due to vasospasm and/or abnormal microvascular vasodilatation, developing invasive/non-invasive testing and treatment protocols, integrating diagnostic protocols into cardiologists' workflow and trials to inform guideline development were identified as key knowledge gaps and will be briefly addressed in this Viewpoint article.
Setting: Virtual international meeting.
Participants: Leading international experts in ischemic heart disease with no obstructive coronary artery disease.
Interventions: None.
Main outcome measures: None.
Results: Topics discussed include: 1. Obstructive epicardial disease, functional vasospasm and microvascular disorders; 2. Under-recognition of coronary vasomotor disorders in clinical practice; 3. Complexity of coronary vasomotor disorders; 4. Understanding different presentations - vasospastic disease and microvascular angina; 5. Invasive/noninvasive testing and treatment protocols for vasospasm and microvascular angina assessment; 6. Treatment challenges; 7. Integrating diagnostic protocols into cardiologists' workflow; 8. The path forward to advance our approach to managing myocardial ischemia.
Conclusions: Obstructive epicardial disease, functional vasospasm and microvascular disorders often co-exist and contribute to myocardial ischemia. Under-recognition, the complexity of coronary vasomotor disorders, understanding different presentations, testing and treatment protocols, treatment challenges, and integrating

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; INOCA, myocardial ischemia with no obstructive CAD.

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diagnostic protocols into cardiologists' workflow all contribute to the path forward to advance our management of myocardial ischemia for improved patient outcomes.

1. Obstructive epicardial disease, functional vasospasm and microvascular disorders

Myocardial ischemia may result from both structural (fixed obstructive lesions) and functional (dynamic vasomotor dysfunction) disorders of the epicardial coronary arteries and/or coronary microvascular circulation. Most attention clinically has centered on the diagnosis and treatment of epicardial coronary artery disease (CAD), though stenosis severity does not predict prognosis, and myocardial ischemia with no obstructive CAD (INOCA), defined as the signs and symptoms of ischemia without CAD, is observed in about half of the patients undergoing clinically indicated coronary angiograms [1]. The most common mechanisms responsible for INOCA appear to include coronary artery spasm (epicardial or microvascular) and coronary microvascular disorders alone or in combination. While there is growing scientific and clinical acceptance of INOCA as a distinct entity that is highlighted in cardiology professional society guidelines [1], challenges remain in advancing both the diagnosis and management of patients with INOCA, most of whom are women.

Recently, the Coronary Vasomotor Disorders International Study Group (COVADIS) invited leading experts to address strategies to enhance our clinical understanding of INOCA, with an emphasis on the management of coronary vasomotor disorders. Under-recognition of coronary vasomotor disorders, distinguishing different presentations of angina due to vasospasm and/or abnormal microvascular vasodilatation, developing invasive/non-invasive testing and treatment protocols, integrating diagnostic protocols into cardiologists' workflow and trials to inform guideline development were identified as key knowledge gaps and will be briefly addressed in this Viewpoint article. We emphasize also that epicardial coronary obstruction and INOCA are not mutually exclusive causes of ischemia, and both may coexist clinically—often in the same patient.

Also critically important is the lack of knowledge about the clinical course of INOCA patients that was recently advanced by CIAO-ISCHEMIA, an ancillary study of the ISCHEMIA trial. CIAO ISCHEMIA, by most of the same ISCHEMIA investigators [2], described the natural history of symptoms and ischemia among patients screened for ISCHEMIA with abnormal stress imaging but no obstructive CAD. The outcome of interest was the association between changes in angina (Seattle Angina Questionnaire Angina Frequency score) and changes in echocardiographic wall motion evidence for ischemia. CIAO participants were more often female (66% vs. only 26% of ISCHEMIA participants with obstructive CAD) but the magnitude of ischemia was not different (median 4 ischemic segments) between these cohorts. At enrollment, ischemia magnitude and angina were not significantly correlated in either the CIAO (e.g., INOCA) or ISCHEMIA (obstructive CAD) participants. Unfortunately, follow-up stress echocardiography was not part of ISCHEMIA. But at 1-year, a stress echocardiogram became normal in half of CIAO participants as about a quarter had moderate or severe persisting ischemia, while angina outcomes improved in almost half and worsened in only 14%. Most interesting was the observation that change in ischemia over 1 year was not correlated with change in angina. The investigators concluded that although improvements in ischemia and in angina were common without obstructive CAD, they were not correlated.

These results highlight the complex pathophysiology and the multifactorial mechanisms of ischemic heart disease and the difficulty of attempting to assess outcomes. Mechanisms and diagnostic evaluation of ischemic heart disease in those with or without obstructive CAD and in those with persistent angina following revascularization, and the optimal approach to analyze and manage these patients, represent knowledge gaps for future trials to address.

COVADIS has developed consensus nomenclature statements, created registries, and fostered clinical trials for coronary vasomotor disorders, thereby raising awareness of the importance of coronary vasomotor dysfunction in pathogenesis of angina [3,4]. COVADIS established criteria for vasospastic (Table 1), and microvascular angina (Table 2), and has endorsed performing "functional" angiography vs. only anatomic coronary angiography, quantifying vascular responses in addition to obstructive disease only [1], however other terminologies also exist [5,6]. Pharmacologic trials [1] and the CorMICA randomized trial have suggested treatment targets and approaches for diagnosis and management of patients without obstructive CAD [5], prompting guideline changes [6]. Important challenges remain to better elucidate how best to identify and treat mechanisms of ischemia not necessarily caused by obstructive epicardial CAD and functional coronary disorders.

2. Under-recognition of coronary vasomotor disorders in clinical practice

2.1. Angina following successful coronary revascularization

Many CAD patients, despite technically successful revascularization, develop persistent or recurrent angina and/or ischemia within 1 year, and then often undergo repeat coronary angiography, where typically the stented segment is found to be patent. Frequently, the diagnostic focus pivots away from epicardial CAD to investigations of non-cardiac causes, rather than considering "non-anatomic epicardial" coronary causes of ischemia such as vasomotor dysfunction. This diagnostic "blind spot" often assumes that epicardial CAD is the singular cause of angina and/or ischemia and ignores the likely presence of vasospastic disorders and the microvascular abnormalities that comprise INOCA, which are more commonly at play clinically.

Table 1
Coronary Artery Vasospastic Disorders Summit diagnostic criteria for vasospastic angina[a].

Vasospastic angina diagnostic criteria elements
1. Nitrate-responsive angina—during spontaneous episode, with at least one of the following:
a. Rest angina—especially between night and early morning
b. Marked diurnal variation in exercise tolerance—reduced in morning
c. Hyperventilation can precipitate an episode
d. Calcium channel blockers (but not beta-blockers) suppress episodes
2. Transient ischemic ECG changes—during spontaneous episode, including any of the following in at least two contiguous leads:
a. ST segment elevation ≥0.1 mV
b. ST segment depression ≥0.1 mV
c. New negative U waves
3. Coronary artery spasm—defined as transient total or subtotal coronary artery occlusion (0.90% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)

Abbreviation: ECG, electrocardiogram.

[a] *Definitive vasospastic angina* is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changes during the spontaneous episodes or coronary artery spasm criteria are fulfilled. 'Suspected vasospastic angina' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes but transient ischaemic ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal. Reprinted with permission from Beltrame et al. [3].

Table 2
Clinical criteria for suspecting microvascular angina (MVA)[a].

1. Symptoms of myocardial ischemia

a. Effort and/or rest angina
b. Angina equivalents (i.e. shortness of breath)

2. Absence of obstructive CAD (b50% diameter reduction or FFR N 0.80) by

a. Coronary CTA
b. Invasive coronary angiography

3. Objective evidence of myocardial ischemia

a. Ischemic ECG changes during an episode of chest pain
b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality

4. Evidence of impaired coronary microvascular function

a. Impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤2.5)
b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing.
c. Abnormal coronary microvascular resistance indices (e.g. IMR N 25)
d. Coronary slow flow phenomenon, defined as TIMI frame count N25.

Abbreviations: CAD, coronary artery disease; CTA, computed tomographic angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; TIMI, thrombolysis in myocardial infarction.

[a] *Definitive MVA* is only diagnosed if all four criteria are present for a diagnosis of micro-vascular angina.

Suspected MVA is diagnosed if symptoms of ischemia are present (criteria-1) with no obstructive coronary artery disease (criteria-2) but only (a) objective evidence of myocardial ischemia (criteria-3), or (b) evidence of impaired coronary microvascular function (criteria-4) alone.
Reprinted with permission from Ong et al. [4].

2.2. Chest pain with non-obstructive coronary artery disease

Over 50% of patients undergoing coronary angiography fail to show significant epicardial coronary obstruction. Similarly, rather than undertaking 'functional' angiographic testing to diagnose/exclude coronary vasomotor disorders, many patients are discharged from cardiology practices with a diagnosis of 'non-cardiac chest pain', despite the persistence of ongoing chest discomfort. The prevalence of "normal" functional testing in patients with suspected INOCA is 50–60%.

2.3. Challenges to recognizing coronary vasomotor disorder

These include the inability to easily image functional microvascular disorders and the high prevalence in women who are often erroneously stereotyped as having psychological explanations for angina. While epicardial vasospasm has been accepted for >30 years because it can be visualized at angiography, spontaneous episodes are only sporadically imaged and provocative spasm testing is often required to evaluate the diagnosis. But unfortunately, this is not part of the usual 10-minute clinical invasive coronary evaluation. In contrast, coronary microvascular disorders cannot be visualized (without very specialized computational hemodynamics) but only inferred from a more physiologically based functional assessment.

3. Complexity of coronary vasomotor disorders

Coronary vasomotor disorders are generally only considered in the context of INOCA when the cause(s) for angina and related symptoms are not clear. However, epicardial coronary artery spasm and coronary microvascular dysfunction (CMD) may frequently coexist with obstructive CAD. Indeed, inducible coronary spasm is often localized to site of atherosclerotic plaques. Furthermore, CMD has also been associated with obstructive CAD (Type-3 CMD), as well as myocardial disorders (Type-2 CMD) [6] and both disorders may coexist in the same patients [1]. It is now recognized that functional abnormalities of the coronary circulation likely account for many of the 20–40% of patients with persisting symptoms after technically successful percutaneous coronary interventions [7].

Hence, the binary classification of anatomic epicardial CAD as being separate and distinct from microvascular vasomotor disorders is an oversimplification and error to a more complete scientific understanding of the multifactorial causes of angina and ischemia.

4. Understanding different presentations - vasospastic disease and microvascular angina

A continuing diagnostic challenge is that microvascular spasm or epicardial spasm is best assessed invasively. In many cases, our management is guided by knowledge and common sense about coronary functional disorders. Three components include spasm, impaired dilation, and the so-called "sensitive heart" which may respond to different treatments. If we identify the appropriate mechanism, it becomes easier to target appropriate treatment to the underlying cause.

5. Invasive/noninvasive testing and treatment protocols for vasospasm and microvascular angina assessment

While provocative testing for vasospasm and physiologic testing for vasomotor disorders are important to probe for non-epicardial CAD causes of ischemia, this may pose time and workload constraints in the busy cardiac catheterization laboratory. The fact that acetylcholine and ergonovine, very old agents approved for ophthalmological and postpartum indications, respectively, but not for coronary testing may be an excuse. But this is difficult to understand since many diagnostic and therapeutic practices are either by "consensus" or physician choices in the best interests of the patient.

Advances such as the incorporation of the COVADIS and CorMicA terminology, newer thermodilution catheters, with billing codes that accommodate the extended time for reimbursement issues may address some of these concerns. Similarly, there is need for more reliable noninvasive testing that would distinguish spasm and impaired microvascular vasodilatation that would expedite diagnostic accuracy. Only positron emission tomography and cardiac magnetic resonance imaging are useful for patients with limited flow reserve but cannot detect spasm.

6. Treatment challenges

The multifactorial nature of INOCA makes treatment of these patients challenging. Apart from vasospastic angina, challenges include the absence of a defined treatment for many INOCA patients. Often, sequential, empirical pharmacological and biological trials are necessary; lifestyle changes are difficult to implement, and oftentimes there may be an overlay where symptoms can be either under- or over-interpreted. Furthermore, data from randomized, double blinded, placebo controlled shorter term trials in the NHLBI WISE ancillary studies [8,9] showed improvement in angina and coronary flow reserve with placebo treatment. These randomized, controlled trial data confirm the uncontrolled observations from CIAO-ISCHEMIA. As a result, fine balance exists between patients who have an expectation for a therapeutic "quick-fix" collides with the reality that this could evolve over a long time period and tailoring treatment through sequential trials for INOCA patients may be logistically difficult for many cardiologists. Traditionally, catheterization laboratories are geared primarily to diagnosing obstructive CAD, and probing non-epicardial causes of angina can be challenging. Simpler and better noninvasive tools that are more widely available and easily reproducible would likely enable improved management which, in turn, could lead to more diagnostic precision and targeted therapies.

7. Integrating diagnostic protocols into cardiologists' workflow

Adapting physiologic coronary testing with fractional flow reserve and instantaneous wave-free ratio measurement into routine catheterization laboratory workflow is inconsistent. Despite the lessons learned from trials that physiology-guided revascularization improves symptoms and potentially outcomes, it seems clear that a more comprehensive understanding of patients' ischemic symptoms is needed to know if the problem truly is the epicardial stenosis vs. functional disorders such as vasospasm or impaired microvascular vasodilatation, or a combination. Development of diagnostic pathways including biomarkers is needed. Even when there is flow-limiting epicardial obstruction, percutaneous coronary intervention may ameliorate only the part of the problem that is epicardial in origin. Randomized trials are needed to investigate different diagnostic approaches, including comparative assessment of adenosine and acetylcholine, and therapies for other conditions.

8. The path forward to advance our approach to managing myocardial ischemia

The path forward to meet these challenges will include enhancing communication and clinical trials. While COVADIS has recommended progressive acetylcholine dosing to uncover vasospasm, this has not been widely adopted clinically, and clearly there is an important need to derive evidence from prospective, randomized trials to enable such a more enlightened diagnostic approach to gain more widespread acceptance. Communication between general cardiologists and interventional colleagues to proceed to functional testing when epicardial CAD is excluded may facilitate an improved flow pattern of either general or interventional cardiology.

Further, some patients have non-cardiac causes of chest pain, and this adds to the diagnostic complexity and tension many general cardiologists face: the uncertainty and non-specificity of symptoms that may not correlate with any objective anatomic or physiologic measures of coronary abnormalities and the issue of silent ischemia in asymptomatic individuals with risk factors. Nevertheless, before non-cardiac causes of chest pain are explored such pain perception abnormalities, non-epicardial coronary causes should first be considered and pursued diagnostically.

While the CorMICA approach received a class II indication in European guidelines [6], it represents a good first evidence-based step. A further testable hypothesis is to investigate intensive treatment of coronary atherosclerosis with high-intensity statins, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and low-dose aspirin for improvement of angina and ischemia in women with INOCA. The WARRIOR trial (NCT03417388) is testing whether such treatment translates to improved outcomes, while the Randomized Evaluation of Beta Blocker and ACEI/ARB Treatment in MINOCA Patients - MINOCA-BAT (MINOCA-BAT) (NCT03686696) is evaluating a beta-blocker and ACEI/ARB intervention on major adverse cardiac events. The PRIZE trial (NCT04097314) is evaluating whether treatment with an endothelin A receptor antagonist has disease-modifying potential in microvascular angina with improvements in symptoms and exercise duration.

In summary, obstructive epicardial disease, functional vasospasm and microvascular disorders often co-exist and contribute to myocardial ischemia. Under-recognition, the complexity of coronary vasomotor disorders, understanding different presentations, testing and treatment protocols, treatment challenges, and integrating diagnostic protocols into cardiologists' workflow all contribute to the path forward to advance our management of myocardial ischemia for improved patient outcomes.

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Declaration of competing interest

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