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

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LIST OF ABBREVIATIONS

EAPCI	European Association of Percutaneous Cardiovascular Interventions
INOCA	Ischaemia with Non-Obstructive Coronary Arteries
COVADIS	Coronary Vasomotor Disorders International Study
SDAIC	Scientific Documents and Initiatives Committee
CCS	Chronic Coronary Syndrome
CAD	Coronary Artery Disease
PCI	Percutaneous Coronary Intervention
CFR	Coronary flow reserve
FFR	Fractional Flow Reserve
iwFR	Instantaneous wave free ratio
CMD	Coronary microvascular dysfunction
IHD	Ischaemic Heart Disease
MVA	Microvascular Angina
VSA	Vasospastic angina
WISE	Women's Ischaemia Syndrome Evaluation
SCAAR	Swedish Coronary Angiography and Angioplasty Register
CFVR	Coronary flow velocity reserve
SLE	Systematic lupus erythematosus
TTDE	Transthoracic Doppler echocardiography
MCE	Myocardial contrast echocardiography
PET	Positron emission tomography
CMR	Cardiac magnetic resonance
CCTA	Coronary computed tomographic angiography
GTN	Glyceryl trinitrate
TIMI	Thrombolysis in Myocardial Infarction
FCA	Invasive functional coronary angiography
ACEi	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockade
EECP	Enhanced external counterpulsation
ESC	European Society of Cardiology
IMR	Index of Microcirculatory Resistance (IMR)
US	United States (US)
CABG	Coronary artery bypass surgery
HMR	Hyperemic myocardial velocity resistance
SPECT	Single photon emission computed tomography
HFpEF	Heart failure with preserved ejection fraction
LVEDP	Left ventricular end diastolic pressure
ATP	Adenosine-5′-triphosphate
ACH	Acetylchoine
MI	Myocardial infarction

ABSTRACT

This consensus document, a summary of the views of an expert panel organized by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), appraises the importance of Ischaemia with Non-Obstructive Coronary Arteries (INOCA). Angina pectoris affects approximately 112 million people globally. Up to 70% of patients undergoing invasive angiography do not have obstructive CAD, more common in women than in men, and a large proportion have INOCA as a cause of their symptoms. INOCA patients present with a wide spectrum of symptoms and signs that are often misdiagnosed as non-cardiac leading to under-diagnosis/investigation and under-treatment. INOCA can result from heterogeneous mechanism including coronary vasospasm and microvascular dysfunction and is not a benign condition. Compared to asymptomatic individuals, INOCA is associated with increased incidence of cardiovascular events, repeated hospital admissions, as well as impaired quality of life and associated increased health care costs. This consensus document provides a definition of INOCA and guidance to the community on the diagnostic approach and management of INOCA based on existing evidence from research and best available clinical practice; noting gaps in knowledge and potential areas for further investigation.

PREAMBLE

This consensus document, a summary of the views of an expert panel organized by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), appraises the importance of ischaemia with non-obstructive coronary arteries (INOCA). This document is put together in collaboration with the European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation and endorsed by COVADIS (Coronary Vasomotor Disorders International Study) Group. The EAPCI INOCA consensus document was proposed by the EAPCI Women's Committee and its members. The chairs and writing group task force of this document were selected by the EAPCI Scientific Documents and Initiatives Committee (EAPCI SDAIC) and EAPCI Women's Committee. The writing group task force members are represented from the EAPCI Women's Committee, EAPCI SDAIC, COVADIS Steering Committee/members and European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation. The formal approval for this document was provided by the ESC Clinical Practice Guidelines Committee and coordinated by the EAPCI office. The writing task force members have provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. This consensus document provides a definition of INOCA and guidance to the clinical and research community on the diagnostic approach and management of INOCA based on existing evidence and best current practices, and identifies areas for further investigation.

INTRODUCTION

Angina pectoris, the most common symptom of ischaemic heart disease (IHD), affects approximately 112 million people globally[1]. The 2019 ESC guidelines provides guidance on the diagnosis and management of patients with chronic coronary syndromes (CCS)[2]. A large proportion of patients (up to 70%) undergoing coronary angiography because of angina and evidence of myocardial ischaemia do not have obstructive coronary arteries but have demonstrable ischaemia [2, 3]. Studies carried out in the past 2 decades have highlighted that coronary microvascular dysfunction (CMD) and epicardial vascular dysfunction are additional pathophysiologic mechanisms of IHD[4]. CMD and epicardial vasospasm, alone or in combination with CAD, are adjunctive mechanisms of myocardial ischemia. However, these conditions are rarely correctly diagnosed and, therefore, no tailored therapy is prescribed for these patients. As a consequence, these patients continue to experience recurrent angina with impaired quality of life, leading to repeated hospitalizations, unnecessary coronary angiography and adverse cardiovascular outcomes in the short and long term[5,6]. This consensus document provides a definition of Ischaemia with Non-Obstructive Coronary Arteries (INOCA) and guidance to the clinical community on the diagnostic approach and management of INOCA based on existing evidence and best current practices. Additionally, having a universal definition of INOCA and identifying gaps in knowledge will serve to encourage research to improve outcomes for this patient population. Discussion of angina caused by CMD in the context of cardiomyopathy (hypertrophic, dilated), myocarditis, aortic stenosis, infiltrative diseases of the heart, percutaneous (PCI)/surgical interventions (CABG) and other possible mechanisms[7] (**Figure 1**) such as inflammation, systemic inflammatory or autoimmune disease

(lupus, rheumatoid arthritis), platelet/coagulation disorders, primary metabolic abnormalities as well as by myocardial bridging, is beyond the scope of this consensus document. A failure to diagnose epicardial CAD in a patient with documented angina/ischemia should promote a subsequent search pathway to elucidate INOCA endotypes before a search for non-cardiac causes of chest discomfort is explored.

INOCA ENDOTYPES

In the setting of CCS, a mismatch of demand-supply of coronary artery blood flow may lead to transient or recurrent cardiac chest pain related to myocardial ischaemia due to inadequate cellular availability of adenosine-5′-triphosphate (ATP) [8]. Although obstructive CAD is a frequent and well-acknowledged cause of myocardial ischaemia, many stenoses judged as severe on visual assessment, are not flow-limiting. Functional misclassification of obstructive lesions frequently occurs in the range of 40-80% stenosis severity, being particularly high in case of patients with multiple coronary lesions[9-11]. The most recent ESC guidelines recommend the use of myocardial fractional flow reserve (FFR) or instantaneous wave-free ratio (iwFR) to identify patients at high event risk who will benefit from revascularisation[2]. Cardiac ischaemia may also be caused by vascular dysfunction without obstructive CAD, a condition recently termed INOCA. In INOCA the mismatch between blood supply and myocardial oxygen demands may be caused by CMD and/or epicardial coronary artery spasm, typically in the setting of non-obstructive coronary atherosclerosis[12]. **Figure 2**[13, 14] shows the mechanisms of INOCA. Of note, these mechanisms may also cause ischaemia in patients with concomitant obstructive CAD and atherosclerosis with outward remodeling but these cases are not included in INOCA by definition.

Microvascular Angina

Microvascular angina (MVA) is the clinical manifestation of myocardial ischaemia caused by CMD. In this clinical entity, myocardial ischaemia may result from structural remodelling of the microvasculature (leading to fixed reduced microcirculatory conductance) or vasomotor disorders affecting the coronary arterioles (causing dynamic arteriolar obstruction)[15, 16]. Both vascular dysfunction mechanisms may co-exist and contribute to MVA. An updated standardization of criteria for MVA in patients presenting with angina pectoris or ischaemia-like symptoms in the absence of flow-limiting CAD has been proposed by the COVADIS Group[15] (**Table 1**)**.**

Epicardial vasospastic angina

Vasospastic angina (VSA) is the clinical manifestation of myocardial ischaemia caused by dynamic epicardial coronary obstruction caused by a vasomotor disorder. In 1959, Prinzmetal described the clinical and electrocardiographic manifestations (transient ST segment elevation) of a disorder thought to be due to epicardial coronary artery spasm[17]. Subsequently, other forms of vasomotor disorders causing chest pain with transient ST segment depression or T wave inversion were described. Overall, these clinical entities caused by epicardial vessel spasm were grouped under the term VSA. A standardization of diagnostic criteria for VSA has been previously described by the COVADIS group (**Supplemental Table 1**) [18]. MVA and epicardial VSA can co-exist which is associated with worse prognosis[19].

EPIDEMIOLOGY

Prevalence in the general population and according to sex and age

The majority of patients referred for assessment for angina do not have obstructive coronary arteries. In unselected populations referred for assessment less than 10% have obstructive CAD[3, 20]. In all studies there is a strong female preponderance for the condition. A large US multicentre study showed that nearly 39% of the patients selected for coronary angiography because of suspected angina and/or positive stress test have non-obstructive CAD[21]. This frequency is higher among women (approximately 50 to 70%), compared to men (30 to 50%). In a retrospective registry from Eastern Denmark including 11,223 patients with angina referred for coronary angiography between 1998 and 2009, 65% of women versus 33% of men had non-obstructive CAD, with an increasing rate over the ten-year study period in both sexes, reaching up to 73% among women in 2009.[5] Similarly, almost two-thirds (62%) of women referred for coronary angiography and enrolled in the National Heart, Lung, and Blood Institute-sponsored Women's Ischaemia Syndrome Evaluation (WISE), did not have a significant obstructive stenosis. Women with non-obstructive CAD were younger than those with obstructive CAD.[22]

Prevalence of coronary microvascular dysfunction

The prevalence of CMD in patients with angina and no obstructive CAD undergoing invasive angiography depends on the methods and cut-off applied. In the iPower study 26% of 963 symptomatic women with no obstructive CAD had coronary flow velocity reserve (CFVR) below 2 when assessed by transthoracic Doppler echo[23]. However these studied should be interpreted in the context that non invasive estimation of CFVR has several limitations[24, 25].

Other studies assessing CMD invasively or by positron emission tomography with different cut-offs have found 39% to 54% have CMD[21, 26]. In a large study with invasive assessment of CMD in 1439 men and women with chest pain and no obstructive CAD included over a period of 19 years, 30% had abnormal CFVR in response to adenosine[27].

The association between traditional cardiovascular risk factors and INOCA is not clearly established. Smoking has been associated with CMD[28]. Age, diabetes, hypertension and dyslipidaemia have been shown to be associated with impaired CMD both in the iPower study and WISE study[21, 23]. Other studies have shown that diabetes was uncommon among patients presenting with angina and non-obstructive CAD, while hypertension and dyslipidaemia were relatively more prevalent.[27 29]
CMD is associated with pro-inflammatory markers in women with INOCA[30, 31]. In the WISE cohort, novel risk variables like those associated with inflammation seemed to play a role in CMD[32]. For instance, systematic lupus erythematosus (SLE) and rheumatoid arthritis appear to be associated with CMD and are frequently encountered in patients with angina and CMD[33, 34]. After menopause, inflammatory diseases occur more often in women compared to men, which may contribute to sex-differences in CMD[35]. Although large studies are lacking, there is increasing evidence that psychosocial stress is more involved in coronary vasomotor disorders and variant manifestations of IHD compared to obstructive CAD[36]. These seem to affect men and women differently[37]. Women have elevated levels of high-sensitive C reactive protein (hsCRP), and a lower monocyte and eosinophil count than men. A significant positive association between Beck Depression Inventory cognitive symptoms with elevated hsCRP level is observed in men, but not in women[37].

Prevalence of coronary artery spasm

The Japanese population has a higher prevalence of angina related to coronary vasomotor disorders[38] compared with western populations. In addition, the frequencies of multiple coronary spasm (≥2 spastic arteries) by provocative testing in Japanese (24.3%)[39] and Taiwanese populations (19.3%)[40] are markedly higher than those in Caucasians (7.5%)[41]. Interestingly, VSA is more prevalent among men than women[40]. Most patients with VSA are between 40 and 70 years of age, and the prevalence tends to decrease after the age of 70 years[40]. Previous Asian studies of patients with non-obstructive CAD have shown that the prevalence of coronary vasomotor disorders is around 50% in patients with angina[42, 43]. European studies have also shown a high prevalence of epicardial vasospasm when systematically tested[44, 45]. However, due to differences in stress protocols and definitions applied, the studies are not directly comparable. Female patients were more sensitive to acetylcholine with vasomotor dysfunction occurring at lower acetylcholine doses compared with male patients. Smoking is a risk factor for VSA, unlike diabetes and hypertension, and the relationship with dyslipidaemia is unclear[46, 47].

PATHOPHYSIOLOGY AND ENDOTYPES

Microvascular angina and epicardial coronary artery spasm

In the absence of flow-limiting epicardial stenoses, myocardial ischaemia can result from specific pathways of microcirculatory dysfunction.[16] Two microcirculatory dysfunction endotypes account for most cases of MVA: structural microcirculatory remodelling and arteriolar dysregulation.[16, 48]

(1) Structural remodelling of the coronary microvasculature is associated with a decrease in microcirculatory conductance and impaired oxygen delivery capacity.[49]

This is typically caused by inward remodelling of coronary arterioles, with an increase in wall to lumen ratio, loss of myocardial capillary density (capillary rarefaction) or both.[50] Remodelling may occur as a result of cardiovascular risk factors, atherosclerosis, left ventricular hypertrophy or cardiomyopathies.[50] A direct consequence of these pathological changes is a reduction of the vasodilatory range of the coronary microcirculation, limiting maximal blood and oxygen supply to the myocardium. Furthermore, remodelled arterioles are hypersensitive to vasoconstricting stimuli.[51] The haemodynamic correlates of structural microcirculatory remodelling in response to a non-endothelium-dependent vasodilator, like adenosine, are (i) a reduced coronary flow reserve and (ii) an increase in minimal (hyperaemic) microcirculatory resistance.

(2) Arteriolar dysregulation typically takes place in medium and large size arterioles, in which flow-mediated vasodilation is predominant.[16] Under physiological conditions, an increase in myocardial oxygen consumption generates an upstream vasodilatory cascade in coronary resistance vessels. This is initiated by metabolically-triggered vasodilation of distal arterioles, that are particularly sensitive to certain metabolites, and it is followed by flow-mediated (endothelium-dependent) vasodilation of larger arterioles located upstream, as well as epicardial vessels.[52] In the presence of endothelial dysfunction, dysregulation of the described upstream vasodilatory cascade occurs. Thus, endothelial dysfunction is associated with impaired vasodilation and even paradoxical vasoconstriction of upstream arteries and arterioles when myocardial oxygen demands increase which may be the result of hypersensitivity to vasoconstrictor stimuli[53]. Some of the haemodynamic correlates of arteriolar dysregulation, observed during intracoronary acetylcholine challenge, are (i) a limited vasodilatory response to the drug (less than 1.5 times resting flow), (ii) a marked

reduction in blood flow, equivalent to the no-reflow phenomenon, without epicardial vessel spasm -denoting arteriolar spasm- and (iii) the development of diffuse narrowing of distal epicardial vessels without focal, tight coronary spasm. The above-mentioned changes frequently run along the development of anginal symptoms and ischaemic ECG changes, which confirm the ischaemia-generating potential of this endotype of microcirculatory dysfunction. Effects of fluctuating oestrogen levels on epicardial vessel and arteriolar vasomotion have been postulated as explanations for a higher frequency of symptoms in premenopausal women without obstructive CAD[54]. Epicardial vessel spasm typically has an origin in a hyper-reactive epicardial coronary segment that undergoes maximal contraction when exposed to a vasoconstrictor stimulus.[55] Among such triggering stimuli are smoking, drugs, peaks in blood pressure, cold exposure, emotional stress and hyperventilation. Severe coronary vasospasm may also occur in the context of allergic reactions (Kounis syndrome). Coronary segments adjacent to implanted drug eluting stents may also become prone to undergo coronary spasm.[56] The substrate of coronary spasm can be found in abnormal function of both vascular smooth muscle and endothelial cells. A primary and nonspecific hyper-reactivity of coronary vascular smooth muscle cells has been consistently demonstrated in patients with variant angina and appears to be a key component of epicardial vessel spasm. Available evidence suggests that endothelial dysfunction facilitates the induction of spasm in predisposed coronary segments.[57]

CLINICAL PRESENTATION

Patients with INOCA present with a wide spectrum of symptoms and signs that are often misdiagnosed as of non-cardiac origin, leading to under-investigation and under-treatment (**Supplemental Table 2**). Patients with INOCA may present with symptoms similar to angina occurring with obstructive CAD.[58, 59] INOCA, like obstructive CAD, can also present with other symptoms such as breathlessness, pain between the shoulder blades, indigestion, nausea, extreme fatigue, weakness, vomiting and/or sleep disturbances.

It is important to recognise that there is gender variation in the clinical manifestation of both obstructive and non-obstructive CAD.[60-62] These differences in presentation are of particular relevance in young and middle-aged women and also men[2, 63] who do not present with classical anginal symptoms.[64, 65] With the same symptoms, women are much less likely to have obstructive CAD and much more likely to have CMD as a cause of their symptoms. Additionally, because symptoms may be uncharacteristic, many cases of CMD may go undiagnosed.

Importantly, INOCA is associated with a wide variation in clinical presentation and symptom burden may vary over time. These symptoms should not be automatically classified as non-cardiac in origin, particularly given the fact that women have a much higher prevalence of INOCA than men.[66]

SHORT- AND LONG-TERM PROGNOSIS

The prognosis of patients with INOCA is far from benign. Angina with no obstructive CAD is associated with impaired quality of life for patients[6 67], higher risk of disability [68] as well as a higher incidence of adverse events[5] including increases in mortality, morbidity, and healthcare costs with higher recurrence rates of hospital readmissions

and higher rates of repeated coronary angiograms.[69] [70, 71, 72-74]. In the WISE study, persistent chest pain, smoking, CAD severity, diabetes, and increased QTc interval were significant independent predictors of cardiovascular events defined as CV death, MI, congestive heart failure, or stroke[75]. In a meta-analysis[74], incidence of all-cause death and non-fatal MI in patients with non-obstructive atherosclerosis was much higher (1.32/100 person-years) than in those with angiographically normal epicardial vessels (0.52/100 person-years). Proven myocardial ischaemia by non-invasive imaging techniques (stress echocardiography or nuclear imaging) was associated with a higher incidence of events (1.52/ 100 person-years) compared to ischaemia detected by exercise electrocardiographic stress testing 0.56/100 person-years.

It must be noted, the condition is heterogeneous and not all patients with angina and no obstructive CAD have ischaemia as a cause of their symptoms. However, when ischaemia is documented through CMD or endothelial dysfunction the prognosis is further impaired. Meta-analyses have shown a 2-4 fold higher risk of adverse cardiovascular outcome for patients with CMD diagnosed by PET or TTDE and a 2-fold higher risk in patients with epicardial endothelial dependent dysfunction[67]. VSA is associated with major adverse events including sudden cardiac death, acute MI, and syncope which may unfortunately occur before the diagnosis is established[76-78].

Should the possibility of non-obstructive causes of ischaemia not be considered by the treating physician, a coronary angiogram showing no obstructive disease may be followed by incorrect interpretation of the patient´s symptoms, avoidance of further diagnostic evaluation, and lack of adequate treatment. Indeed, coronary angiography in INOCA showing non-obstructive coronary arteries may result in inappropriate discontinuation of medical therapy, paradoxical reassurance by the treating physician and potentially, the physician may even refute the underlying symptoms. This

approach is not patient-centred, as many will continue to have symptoms that will lead to rehospitalisation, repeated diagnostic testing and inappropriate treatment.

DIAGNOSIS

Non-invasive methods to detect ischaemia

Functional or structural abnormalities of the coronary microcirculation can be responsible for impairment of myocardial perfusion and ischaemia, even in the absence of large epicardial coronary arteries stenosis[13, 14, 79]. Common non-invasive techniques assessing ischaemia rely on detection of relatively large regional differences in left ventricular perfusion and/or wall motion in epicardial perfusion territories (i.e. myocardial single-photon emission computed tomography or dobutamine stress echocardiography). These techniques are ineffective if ischaemia affects the whole left ventricle as in patients with CMD[80, 81]. Currently, no technique allows a direct anatomical visualization of the coronary microcirculation *in vivo* in humans. Therefore, its assessment relies on the measurement of parameters which reflect its functional status, such as myocardial blood flow and coronary flow reserve (CFR).

CFR is the ratio of hyperaemic blood flow in response to various vasoactive stimuli divided by resting blood flow. CFR is an integrated measure of flow through both the large epicardial arteries and the coronary microcirculation, but once severe obstructive disease of the epicardial arteries is ruled out, reduced CFR is a marker of CMD. The maximal vasodilatation and hyperaemia necessary to calculate the CFR is usually achieved through intravenous administration of endothelium-independent vasodilators such as adenosine, or regadenoson[21].

In the diagnostic pathway for patients assessed for angina recommended in the ESC CCS 2019 guideline[2], first line of testing is non-invasive. In patients with no obstructive CAD on their CCTA (Coronary Computed Tomographic Angiography) and/or no regional reversible ischaemia on functional testing, CMD or VSA may be the cause of their symptoms and in patients with a significant burden of disease, further testing through non-invasive and invasive techniques should be considered. While non-endothelial dependent dysfunction may be assessed non-invasively, acetylcholine can only be administered during invasive testing. Thus, a full diagnostic assessment for INOCA currently requires invasive angiography. Several non-invasive techniques allow assessment of CFR (**Figure 3**, **Supplemental Table 3**)

Invasive diagnosis in the catheterization laboratory

The 2019 ESC CCS guidelines[2] have given a IIa recommendation ("should be considered") for guidewire-based measurement of CFR and/or microcirculatory resistance measurements in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with non-flow limiting disease. Intracoronary acetylcholine (ACH) testing is supported by a IIb recommendation "may be considered" to assess coronary microvascular spasm and for patients in whom VSA is considered, a IIa recommendation to clarify both endothelium-dependent as well as endothelium-independent pathobiologic mechanisms of CMD.

Diagnostic testing provides information on coronary vascular dysfunction, including a functional disorder i.e. impaired vasodilatation, or vasospasm, and/or structural problem i.e. an increase in minimal vascular resistance. Relevant endotypes include 1) MVA, 2) VSA, 3) both, 4) none i.e. non-cardiac chest pain, and 5) non-flow-limiting

CAD e.g. diffuse atherosclerosis, <50% stenosis severity by visual assessment. A clinical diagnosis may be according to expert consensus criteria[15]. The diagnostic criteria are shown in **Table 2**. Catheter-based measurements of absolute coronary blood flow and microvascular resistance have also been previously described which requires further evaluation in INOCA patients[82].

Coronary angiography

Glyceryl trinitrate (GTN) has a short half-life and is preferred during coronary angiography. A corrected Thrombolysis in Myocardial Infarction (TIMI) frame count >27 (images acquired at 30 frames/sec)[83] in the presence of GTN suggests MVA due to impaired resting flow (coronary slow-flow phenomenon)[15]. Slow-flow points to an increase in vascular resistance under resting conditions.

Invasive functional coronary angiography

Invasive functional coronary angiography (FCA) is a combinatory technique involving direct invasive measurements of coronary vasomotor function initially with a diagnostic guidewire in combination with pharmacological reactivity testing (**Figure 4**)[84]. Different approaches may slightly vary according to local experience and preference[55, 84-87].

Diagnostic guidewire

Coronary function testing using a diagnostic guidewire is performed as an adjunct to coronary angiography. The left anterior descending coronary artery is usually preferred as the pre-specified target vessel reflecting its subtended myocardial mass and coronary dominance. Additional studies in other coronary arteries may be appropriate if the initial tests are negative and clinical suspicion is high. Intravenous heparin (50–70 U/kg) should be administered to achieve therapeutic anticoagulation

(activated clotting time ~250s). Diagnostic options include coronary thermodilution using a pressure-temperature sensor guidewire (PressureWire X™, Abbott Vascular, Santa Clara, CA) or a Doppler technique (ComboWire XT or Flowire, Philips Volcano Corporation, San Diego, CA). The ComboWire XT connects to the ComboMap system (Philips, Eindhoven). The usual approach to inducing steady-state hyperaemia is by use of intravenous adenosine (140 µg/kg/min) to achieve endothelium independent vasodilation[88]. Intracoronary bolus injection of adenosine (up to 200 µg) is an alternative option to assess endothelium-independent vasodilatation.

Coronary flow reserve (CFR) can be calculated using thermodilution (as resting mean transit time divided by hyperaemic mean transit time)[89, 90] or Doppler flow velocity (hyperaemic flow velocity divided by resting flow velocity)[91]. Overall, most studies demonstrating the prognostic value of thermodilution-based CFR have used a cut-off value of 2.0[92, 93], while studies showing a prognostic impact of CFR based on Doppler have used a CFR cut-off of 2.5 or lower[27, 94, 95].

Microcirculatory resistance can be calculated by combining pressure and flow measurements (either thermodilution- or Doppler-based). The index of microvascular resistance (IMR) is calculated as the product of distal coronary pressure at maximal hyperemia multiplied by the hyperemic mean transit time[96]. Increased IMR (≥25) is representative of microvascular dysfunction[97]. The hyperemic myocardial velocity resistance (HMR) index is a Doppler-based index, calculated by dividing intracoronary pressure by hyperemic flow velocity. In a previous study of patients with angina and non-obstructed coronary arteries, HMR > 1.9 (Odds Ratio: 15.6 [95% Confidence Interval 2.1, 114.0], p = 0.007) was an independent predictor of recurrent chest pain[98]. Other studies have suggested that a cut-off of ≥2.5 mmHg/cm/s provides the optimal sensitivity and specificity for predicting CMD, as judged with PET [99]. Further studies

are required to determine the optimal HMR index that would predict CMD.

Flow-limiting obstructive CAD may be assessed using FFR which is the ratio of mean distal coronary pressure to mean aortic pressure at maximal hyperaemia - abnormal FFR is defined as ≤0.80[100] or a non hyperaemic pressure ratio ≤0.89[100-102]. The binary thresholds of continuous data should be viewed within the context of the patient. CFR, IMR and FFR have prognostic significance across the diagnostic range of their values. Thus, in this invasive evaluation it is possible to determine endothelium-independent CMD (CFR, IMR); endothelium-dependent CMD (microvascular response to ACH) and vasospastic response (epicardial artery response to ACH) as well as an assessment of low grade stenoses (FFR).

Pharmacological invasive functional coronary angiography

The most established approach for vasoreactivity testing is by intra-coronary infusion of acetylcholine[55, 84-87, 103-108], which influences coronary vascular tone via muscarinic receptors on endothelial and vascular smooth muscle cells. The use of intracoronary acetylcholine for the diagnosis of MVA and VSA is recommended by the 2019 ESC CCS clinical practice guidelines[2] on the grounds of its demonstrated safety and efficacy[109]. A pragmatic approach for FCA according to whichever protocol works best in individual centres might be implemented. A standard approach involves sequential infusion of acetylcholine at concentrations approximating 10^{-6}, 10^{-5}, and 10^{-4} mol/L, respectively (**Supplemental Table 4**). A clinical diagnosis to rule-in or rule-out MVA and/or VSA due to vasospasm is made according to established criteria[15, 55]. **Figure 4** shows the steps in the invasive evaluation of INOCA. Based on current practice, steps 1, 2, 3 as shown in **Figure 4** are suggested though some institutions might prefer steps 1, 3, 2 in the invasive evaluation of INOCA. Further studies are warranted to

determine the best sequence of invasive evaluation in the diagnosis of INOCA. The complications and risks of invasive coronary procedures are previously well described[110, 111]. The potential risk of the invasive assessment should be weighed against the benefit of the diagnosis for the patient, acknowledging that so far it has not been studied whether management based on information gathered by invasive diagnostics may influence prognosis while only one small-size trial (CORMICA) has found a benefit in terms of symptoms.

MANAGEMENT OF INOCA

Management should be patient-centred with a multidisciplinary care approach might be helpful to the patient. Unfortunately, studies on therapy to improve CMD are small and heterogeneous in design and methodology and currently there is no evidence-based treatment of CMD[112]. There is a strong need for well-designed clinical trials to guide future research and clinical recommendations. **Figure 5** provides an algorithm for the management of INOCA.

Life style factors

In all patients with established INOCA due to the frequent presence of coronary atherosclerosis and endothelial dysfunction[12, 113], tailored counselling on life-style factors is warranted to address risk factors, reduce symptoms and improve quality of life and prognosis. Behavioural interventions can be supported by nurse practitioners, experts in nutrition, psychologists, exercise physiotherapists, sports medicine etc. Adequate life-style support is comparable to other CVD prevention guidelines and preventive strategies in patients with stable CAD.[59, 114] The ability of specific diets, such as anti-inflammatory, vegan or Mediterranean, to improve symptomatic coronary

vascular dysfunction is unknown. However, obesity should be addressed. Coping with stress, the chronic and recurrent nature of symptoms may need extra attention, as they may have an important impact on working abilities in this often relatively young patient group.

Risk factor management

The traditional CVD risk factors hypertension, dyslipidaemia, smoking and diabetes may all contribute to the pathology of coronary microvascular and vasospastic dysfunction and structural remodelling of the circulation. The main therapeutic objective of strict control of blood pressure (BP) is to prevent progression of microvascular changes and to reduce the frequency and intensity of anginal symptoms.[115] Best choice of (combined) BP medications depends on the predominant mechanism of anginal symptoms e.g. vasospastic and/or MVA. The use of angiotensin converting enzyme inhibitors (ACEi) improves CFR in CMD[116] and ACEi/angiotensin receptor blockade (ARB) can be easily combined with both calcium-antagonists and beta-blockers.[59, 108, 117, 118] Statins are beneficial in patients with non-obstructive CAD, and their anti-inflammatory properties may also be effective in those patients with reduced CFR and vascular spasm.[119-121]

Antianginal medication

Treatment of anginal symptoms in patients with INOCA is challenging as the patients represent a heterogeneous group and randomized trials are lacking. Standard pharmacological anti-ischemic treatment often achieves disappointing results.[122] The efficacy of short acting nitrates may vary and often needs to be repeated. Long acting nitrates are frequently ineffective, poorly tolerated and may aggravate symptoms in

patients with MVA due to a stealing effect.[59, 123] In patients with evidence of either epicardial or microvascular spasm following acetylcholine testing, calcium antagonists should be considered as first line therapy. In patients with severe VSA it may be needed to give unusual high dosages of calcium antagonist (2x 200 mg diltiazem daily), or even a combination of hydropyridine (such as diltiazem) with dihydropyridine calcium blockers (such as amlodipine), **Table 3**. In patients with MVA and reduced CFR and/or increased IMR (that may reflect arteriolar remodelling) beta-blockers, calcium channel blockers and ACEi are used. [124] ACEi have been demonstrated to improve hyperaemic myocardial blood flow in hypertensive MVA patients,[125] and in women with CMD with improved CFR and angina frequency[116]. In the CorMicA trial, a stratification based medical therapy was used, taking into account the measurements at coronary testing and the approach was shown to improve angina control and quality of life in patients with no obstructive CAD at 6 months and at 1 year.[84, 126].

In perimenopausal women without obstructive CAD, a combined regimen of a low dose alpha-beta blocker or selective beta-blocker (nebivolol, bisoprolol) and calcium antagonist (diltiazem) can be highly effective in reducing anginal symptoms, as the loss of oestrogens often induces autonomic dysfunction with a fast rise in heart rate during exercise[127].

The use of nicorandil, a combinatorial vasodilator agent acting via nitrate and potassium channel activation, may be an effective alternative although side effects are often reported.[128] First line therapy can also be combined with the use of ranolazine, an anti-anginal agent which improves myocyte relaxation and ventricular compliance by decreasing sodium and calcium overload.[129] In patients with MVA mixed beneficial results of ranolazine have been published, demonstrating benefit in patients with low CFR.[130, 131] Some patients with persistent anginal symptoms may benefit from the use

of ivabradine, which decreases heart rate both at rest and during exercise without affecting LV contractility. However, its efficacy in MVA is poorly investigated and still controversial.[132, 133] Rho kinase inhibitors reduce contractility in the vascular wall and are currently under investigation for reducing coronary vasoreactivity.[134] The use of low dose tricyclic antidepressants, such as imipramine, may be helpful to reduce the intensity of symptoms.[108, 117, 118] However, it should be noted that there is currently no evidence-based medication for INOCA and aggravated nociception.[112] Therefore we recommend anti-anginals as currently stipulated in the updated 2019 ESC CCS guidelines which provides a stepwise strategy for anti-anginal drug therapy. The CCS guidelines also recommend trimetazidine as a second-line drug in patients with CCS whose symptoms are not adequately controlled by, or who are intolerant to, other medicines for angina pectoris[2]. In about 25% of patients, symptoms are refractory to these treatment options. Enhanced external counterpulsation (EECP) might be used as an adjunctive treatment for INOCA only in CCS patients who are refractory to both traditional antianginal drugs (beta blockers, calcium channel blockers, nitrates, etc.) as well as more novel interventions such as ranolazine, trimetazidine, and ivabradine[135].

GAPS IN KNOWLEDGE AND FUTURE STUDIES

The key messages are shown in **Table 4 and Figure**. It is evident that INOCA is not often correctly diagnosed and that, as a consequence, no tailored therapy is prescribed for these patients who are often dismissed as “false positive”. Consequently, these patients will continue to experience recurrent angina with poor quality of life, leading to repeated hospitalizations and unnecessary coronary angiography[21, 136], as well as poor clinical outcome. There is an urgent need of large

studies designed to address this problem as shown in **Tables 5 and 6**. The CorCTCA trial (NCT03477890) is ongoing and will help clarify the prevalence and clinical significance of INOCA using coronary CT angiography[137]. To date there are no disease-modifying therapies specific to INOCA. The Women's IschemiA Trial to Reduce Events in Non-ObstRuctIve CORonary Artery Disease is currently enrolling subjects, (WARRIOR: NCT03417388) in a multicenter, prospective, randomized blinded outcome evaluation, to evaluate intensive statin and ACEI/ARB therapy (IMT) and usual care (UC) on major adverse cardiovascular events in symptomatic women with INOCA. The Precision Medicine With Zibotentan in Microvascular Angina (PRIZE) trial holds future promise (ClinicalTrials.gov Identifier: NCT04097314). Zibotentan is an oral, endothelin A receptor antagonist that may provide benefit by opposing the reported increase in vasoconstrictor response of coronary microvessels to endothelin[53].

CONCLUSIONS

INOCA, a major health problem, is associated with under diagnosis, under-treatment and poor prognosis. This consensus document provides the treating clinician/interventional cardiologist guidance regarding the recommended diagnostic/investigational approach and the management of INOCA based on the existing evidence and the best available current practice. Future prospective well-designed ongoing research is required to address a number of unanswered questions in the diagnosis and management of these patients.

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List of Tables

Figure legends

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