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Novel diagnostic approaches and management of coronary microvascular dysfunction

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ABSTRACT

The mechanism underlying ischaemic heart disease (IHD) has been primarily attributed to obstructive coronary artery disease (CAD). However, non-obstructive coronary arteries are identified in >50% of patients undergoing elective coronary angiography, recently leading to growing interest in the investigation and management of angina/ischaemia with non-obstructive coronary arteries (ANOCA/INOCA). INOCA is an umbrella term encompassing a multiple spectrum of possible pathogenetic entities, including coronary vasomotor disorders which consist of two major endotypes: coronary microvascular dysfunction (CMD) and vasospastic angina. Both conditions can coexist and be associated with concomitant obstructive CAD. Particularly, CMD refers to myocardial ischaemia due to reduced vasodilatory capacity of coronary microcirculation secondary to structural remodelling or impaired resting microvascular tone (functional) or a combination of both. CMD is not a benign condition and is more prevalent in women presenting with chronic coronary syndrome compared to men. In this setting, an impaired coronary flow reserve has been associated with increased risk of major adverse cardiovascular events. ANOCA/INOCA patients also experience impaired quality of life and associated increased healthcare costs. Therefore, research in this scenario has led to better definition, classification, and prognostic stratification based on the underlying pathophysiological mechanisms. The development and validation of non-invasive imaging modalities, invasive coronary vasomotor function testing and angiography-derived indices provide a comprehensive characterisation of CMD. The present narrative review aims to summarise current data relating to the diagnostic approach to CMD and provides details on the sequence that therapeutic management should follow.

List of abbreviations: INOCA, Ischaemia with non-obstructive coronary arteries; ANOCA, Angina with non-obstructive coronary arteries; MVA, Microvascular angina; CMD, Coronary microvascular dysfunction; CCS, Chronic coronary syndrome; NSTEMI, Non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; CBF, Coronary blood flow; VSMC, Vascular smooth muscle cell; CFR, Coronary flow reserve; IMR, Index of microvascular resistance; HMR, Hyperaemic microvascular resistance; RRR, Resistance reserve ratio; MRR, Microvascular resistance reserve; mMR, Minimal microvascular resistance; Q, Absolute coronary blood flow; Rμ, Absolute microvascular resistance.

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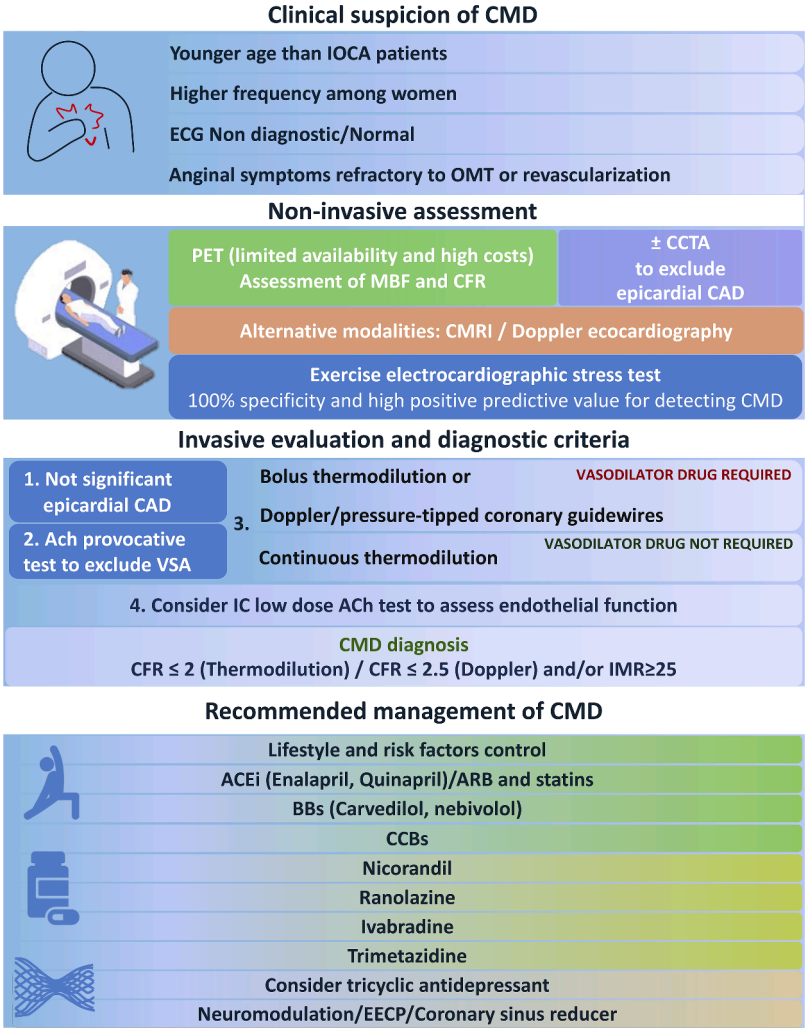
Central illustration. Summary of diagnostic and therapeutic recommendations for CMD. Abbreviations: CMD, coronary microvascular dysfunction; IOCA, ischaemia with obstructive coronary arteries; ECG, electrocardiogram; OMT, optimal medical therapy; PET positron emission tomography; MBF, myocardial blood flow; CFR, coronary flow reserve; CCTA, cardiac computed tomography angiography; CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; ACh, acetylcholine; VSA, vasospastic angina; IC, intracoronary; IMR, index of microcirculatory resistance; ACEi, Angiotensin converter enzyme inhibitors; ARB, angiotensin receptor blockers; BBs, beta-blockers; CCBs, calcium channel blockers; EECP, enhanced external counter pulsation.



1. Introduction

Ischaemic heart disease (IHD) remains a leading cause of morbidity and mortality worldwide. [1] Historically, the mechanism underlying IHD has been primarily attributed to obstructive coronary artery disease (CAD). However, mounting evidence recognises angina/ischaemia with non-obstructive coronary arteries (ANOCA/ INOCA) as major contributors of IHD. [2] Non-obstructive coronary arteries is identified in >50% of patients undergoing elective coronary angiography and is associated with an increased risk of major adverse cardiovascular events (MACE). [3] ANOCA refers to the presence of signs/symptoms of angina with normal or non-obstructive coronary arteries, but no confirmation of myocardial ischaemia by functional non-invasive imaging testing. Whereas INOCA refers to signs/symptoms of stable angina, normal/non-obstructive coronary arteries on angiography, and confirmed presence of myocardial ischaemia.

While obstructive CAD is more common in men, studies consistently underscore a predominance of non-obstructive coronary arteries in women. [4] In the absence of epicardial coronary stenoses >50 %, the mismatch between myocardial oxygen demand and blood supply can result from different mechanisms, including the broad spectrum of coronary vasomotor disorders. The endotypes recognised as major causes for INOCA are coronary microvascular dysfunction (CMD), which is the inability of the coronary vasculature to adequately augment coronary blood flow to match the myocardial oxygen demand in the absence of epicardial CAD, and vasospastic angina (VSA), also called epicardial spasm. [5] Spasm of the coronary microcirculation is termed microvascular spasm. Microvascular angina (MVA) is an umbrella term referring to symptomatic manifestation of ischaemia stemming from disorders of the coronary microcirculation. A meta-analysis investigating CMD and VSA prevalence in 14,427 INOCA patients revealed a significant proportion of patients had CMD (pooled prevalence of 41 %).

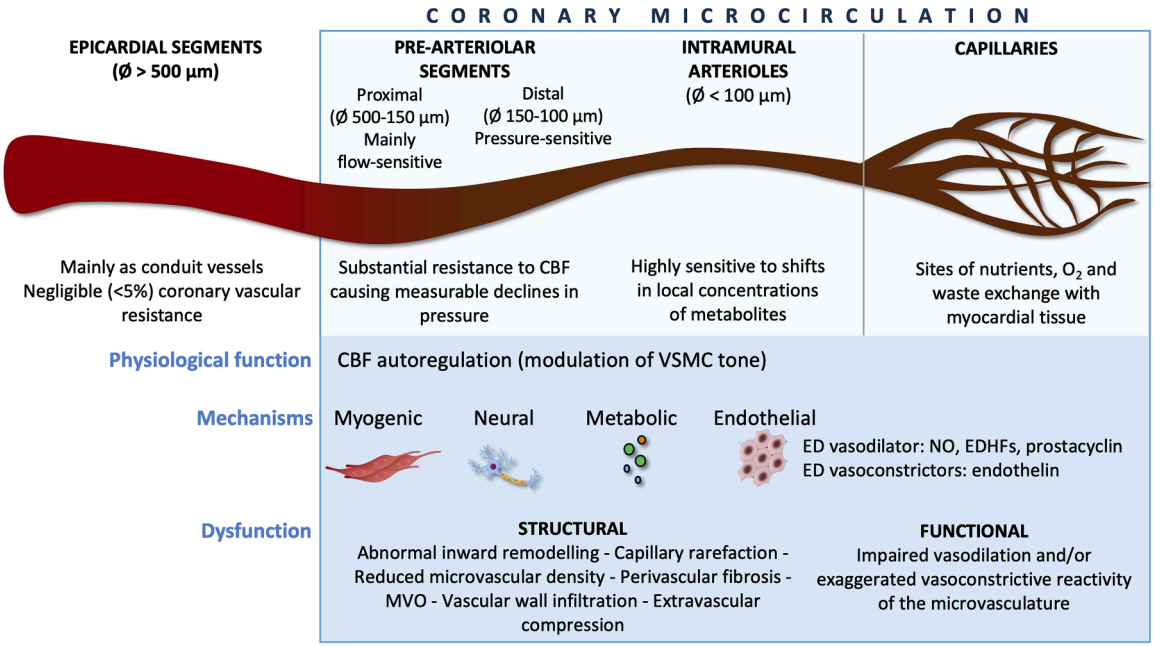


Fig. 1. Autoregulation of CBF and CMD mechanisms.
Abbreviations: Ø, diameter; µm, micrometres; CBF, coronary blood flow; O_2, oxygen; VSMC, vascular smooth muscular cell; ED, endothelium-dependent; NO, nitric oxide; EDHFs, endothelium-derived hyperpolarizing factors; MVO, microvascular obstruction; CMD, coronary microvascular dysfunction.

[6] Furthermore, women were 1.45 times more likely to be diagnosed with CMD than men. [6] However, with many patients experiencing persistent symptoms, CMD represents a therapeutic challenge. The present narrative review aims to summarise current data relating to the diagnostic approach to CMD and provides details on the sequence that therapeutic management should follow.

2. Pathophysiology of CMD

2.1. Physiological autoregulation of coronary blood flow

Coronary arteries are classified into two compartments: epicardial segments and coronary microcirculation. The latter comprises pre-arterioles, arterioles and capillaries. [7] Arterioles and pre-arterioles are responsible for maintaining a steady coronary blood flow (CBF) by regulating coronary vascular resistance (Fig. 1). These vessels regulate CBF by modulating their vascular smooth muscle cell (VSMC) tone to meet oxygen demands. Coronary autoregulation includes myogenic, neural, metabolic, and endothelial mechanisms - the latter being important in CMD. In response to chemical, mechanical, and neurohormonal stimuli, coronary endothelium synthesises vasoactive factors to modulate VSMC tone. Relaxation of the microcirculation induced via endothelial and non-endothelial pathways leads to an increase in CBF.

2.2. Structural and functional CMD

Coronary microvascular dysfunction is characterised by an inability to adequately augment coronary blood flow and the hallmark is an impaired coronary flow reserve (CFR) in response to adenosine. Recent studies have demonstrated that CMD itself may be a heterogeneous condition comprising two distinct endotypes, namely structural and functional CMD; [8-10] whilst both endotypes demonstrate a high prevalence of inducible ischaemia and maladaptive exercise physiology (i.e., a similar core phenotype), they differ in their underlying pathobiology and are clinically distinguished by measuring the minimal microvascular resistance. Structural CMD is characterised by an elevated minimal microvascular resistance, which may be secondary to architectural changes within the microvasculature (such as capillary rarefaction) or impaired endothelial nitric oxide (NO) synthase function; this leads to normal resting coronary blood flow but impaired ability to adequately augment coronary blood flow in response to stress. [10] Functional CMD, on the other hand, is characterised by normal minimal microvascular resistance; these patients have a sub-maximally vasodilated state at rest and, as a result, cannot further augment their coronary blood flow adequately during stress. [8] It remains unknown whether the abnormal resting state is an appropriate response to heightened resting myocardial oxygen demand or if it is due to disorder autoregulation of neuronal NO synthase, which regulates basal coronary flow. Patients with an impaired CFR exhibit a high risk of MACE. Conversely, an impaired microvascular resistance was not associated with adverse prognosis. [8,11] From a therapeutic perspective, structural CMD may benefit from interventions improving afterload-reduction and vascular remodelling, whereas therapies for functional CMD target improvement in basic myocardial metabolism. [8] Mechanisms causing impaired vasodilatory responses can be subdivided into endothelium-dependent and endothelium-independent. Endothelial dysfunction is the main pathological process causing abnormal endothelium-derived (ED) vasodilatory responses (Fig. 1).

3. Molecular, inflammatory, and other mechanisms

A crucial mechanism implicated in the development of CMD is oxidative stress. Elevated levels of reactive oxygen species lead to uncoupling of the nitric NO synthase, which results in attenuated NO bioavailability. Furthermore, oxidative stress induces pro-inflammatory cytokine transcription and immune cells activation. Recent evidence shows a positive association between inflammation, CMD, and perivascular adipose tissue, a metabolically active tissue adherent to blood vessels. [12] In CMD patients, epicardial perivascular adipose tissue is significantly thicker than patients without CMD. [13] CMD is an independent predictor for worse prognosis in patients with heart failure with preserved ejection fraction. [14] A recently proposed pathogenic mechanism involves reduction of pericytes. Upon exposure to oxidative stress, these mural vascular cells induce a pro-inflammatory phenotype in endothelial cells. [15]

4. Risk factors

Numerous studies report a positive association between CMD and some traditional cardiovascular risk factors, showing a difference in the risk profile between structural and functional CMD. Rahman et al. found a higher prevalence of hypertension and diabetes mellitus, as well as exercise-induced hypertension, in patients with structural CMD compared to those with functional CMD. [10] Conversely, cigarette smoking has been reported as the most important risk factor for VSA, especially in young women. [16]

The Women's ischaemia Syndrome Evaluation (WISE) and WISE-Coronary Vascular Dysfunction (WISE-CVD) studies investigated CMD in two cohorts of women with INOCA at different times (1997–2001 and 2009–2011, respectively). The burden of functional CMD were similar in both cohorts (CFR <2.5 was detected in 48 % of WISE patients and 40 % of WISE-CVD patients), although women enrolled in the WISE-CVD cohort had a significantly lower prevalence of traditional cardiovascular risk factors (hypertension, hyperlipidaemia and smoking). This suggests that conventional risk factors may not fully explain abnormalities in coronary microvasculature. [17,18]

5. Ageing, systemic inflammatory conditions

Ageing-related alterations in arterial structure, such as augmented arterial stiffness, partially contribute to worsening CFR and vulnerability to myocardial ischaemia. [19] Growing evidence highlights the positive association of CMD to autoimmune/inflammatory conditions. Psoriasis, systemic lupus erythematosus, and rheumatoid arthritis are commonly observed in CMD patients. [20] This population also faces excessive cardiovascular disease (CVD) risk associated with increased mortality and MACE. [21] The WISE-CVD study reported that in women with CMD, women with autoimmune rheumatic diseases had reduced myocardial perfusion reserve and a trend towards more angina. [22] Furthermore, increased levels of pro-inflammatory markers, higher amongst women compared to men, are linked to CMD. The most robust data pertains to C-reactive protein. [23] Other biomarkers include adhesion molecules and tumour necrosis factor-alpha.

6. Psychological stress

Mounting data delineate the role of psychological stress in advancing disorders of coronary microvasculature. In a study of non-obstructive coronary arteries, patients were divided into an anxiety and non-anxiety group based on the Self-rating Anxiety and Self-rating Depression Scales. Results demonstrated that anxiety was independently associated with a lower CFR, the hallmark of CMD. [24] Similarly, Sara et al. assessed coronary endothelial dysfunction in INOCA patients stratified by sex and the diagnosis of an anxiety disorder. Coronary endothelial dysfunction was significantly more prevalent in patients with anxiety disorders, which persisted in women but not in men, suggesting a higher risk of mental stress-induced CMD in women. [25] In response to stress, hormones, pro-inflammatory markers, and endothelin-1 (ET-1) are released, which inhibit NO and downregulate NO synthase expression. [26] Moreover, in chronically stressed/depressed individuals, an overactive renin-angiotensin-aldosterone system leads to vascular remodelling and reactive oxygen species generation. [27]

7. Sex-Specific differences

Men have a greater cardiovascular risk than women until women reach menopause. Following menopause, CVD incidence in women increases rapidly, outpacing that of men. [28] Oestrogen contributes to regulating VSMC tone by augmenting NO production, enhancing NO action, and lowering circulating ET-1. However, after menopause, oestrogen levels drop. This could explain why premenopausal women have nearly a two-fold improved CBF response compared to postmenopausal women and age-matched men. [29] In postmenopausal women, hormone replacement therapy was not associated with an improvement of invasively assessed coronary endothelial dysfunction. [30] The postmenopausal period exacerbates this sex-related difference, as the increased deposition of adipose tissue amplifies the synthesis of pro-inflammatory cytokines. [31] It is frequently observed that the index of microcirculatory resistance is similar between the two sexes, whereas CFR is lower in women. The latter could be explained by a decreased augmentation of coronary flow from rest to hyperaemia due to impaired microvascular dilatation or by a higher coronary resting flow in women. [32] The association with migraines, hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension) and depression/anxiety emphasize the need to investigate emerging non-traditional sex-specific risk factors. [33] Migraines history has been reported in half of women with suspected INOCA, and women with migraines are younger and complain of worse anginal symptoms, triggered by emotional stress or extreme temperatures, compared to those without migraines. [34]

8. Prognosis

Two recent meta-analyses found an increased risk of MACE and mortality in patients with CMD and non-obstructive coronary arteries compared to those with normal microvascular function. [35,36] Additionally, regardless of sex, low CFR was associated with poorer prognosis in patients with non-obstructive coronary arteries compared to normal CFR. [36] This correlation between low CFR and worse outcomes is important because women generally have a lower CFR than men, which exacerbates sex-related prognostic inequalities. [37] A prognostic link between CMD and outcomes of interventional procedures, e.g. percutaneous coronary intervention (PCI), has been analysed. Pre-existing CMD may decrease tolerance to any ischaemic or mechanical insult following PCI. [38] Similarly, an elevated microvascular resistance post-PCI is a significant predictor of PCI-associated cardiac injury and other adverse outcomes [39]. In patients with epicardial CAD, angina recurrence has been reported in a range between 20 % and 30 % within 1 year after successful revascularisation, leading often to repeated coronary angiography. [40] In this setting, it is essential to consider concomitant non-obstructive causes of angina to be investigated, in order to optimise medical therapy directed at treatment of coronary vasomotor disorders.

9. Non-invasive assessment

Although CMD may occur both in the presence or absence of obstructive CAD, it is simpler to study this phenomenon in the latter since both ischaemia and an abnormal CFR may arise from obstructive CAD per-se. Coronary computed tomography angiography can exclude obstructive CAD so that the demonstration of myocardial ischaemia, impaired perfusion or abnormal CFR can be attributed to CMD. Amongst available options, the most accurate and validated imaging modality is cardiac positron emission tomography (PET). [41] Blood flow through coronary microvasculature is quantified using CFR, defined as the maximum achievable increase in CBF from resting state to maximal vasodilation. [42] Although biological and methodological factors affect quantification of PET-derived indices, it is well established that CFR < 2 confers major risk of death and cardiovascular events. [43] PET usage is often restricted by its limited availability and high costs. Recent improvements in non-invasive testing encompass automated, pixel-wise quantitative mapping of myocardial perfusion by cardiac magnetic resonance imaging (CMRI), acquired during vasodilator stress and resting conditions. Calculation of myocardial perfusion reserve is performed in a similar way to PET, against which it has already been validated. [44,45] The 2021 American College of Cardiology/American Heart association (ACC/AHA) guidelines for the Evaluation and

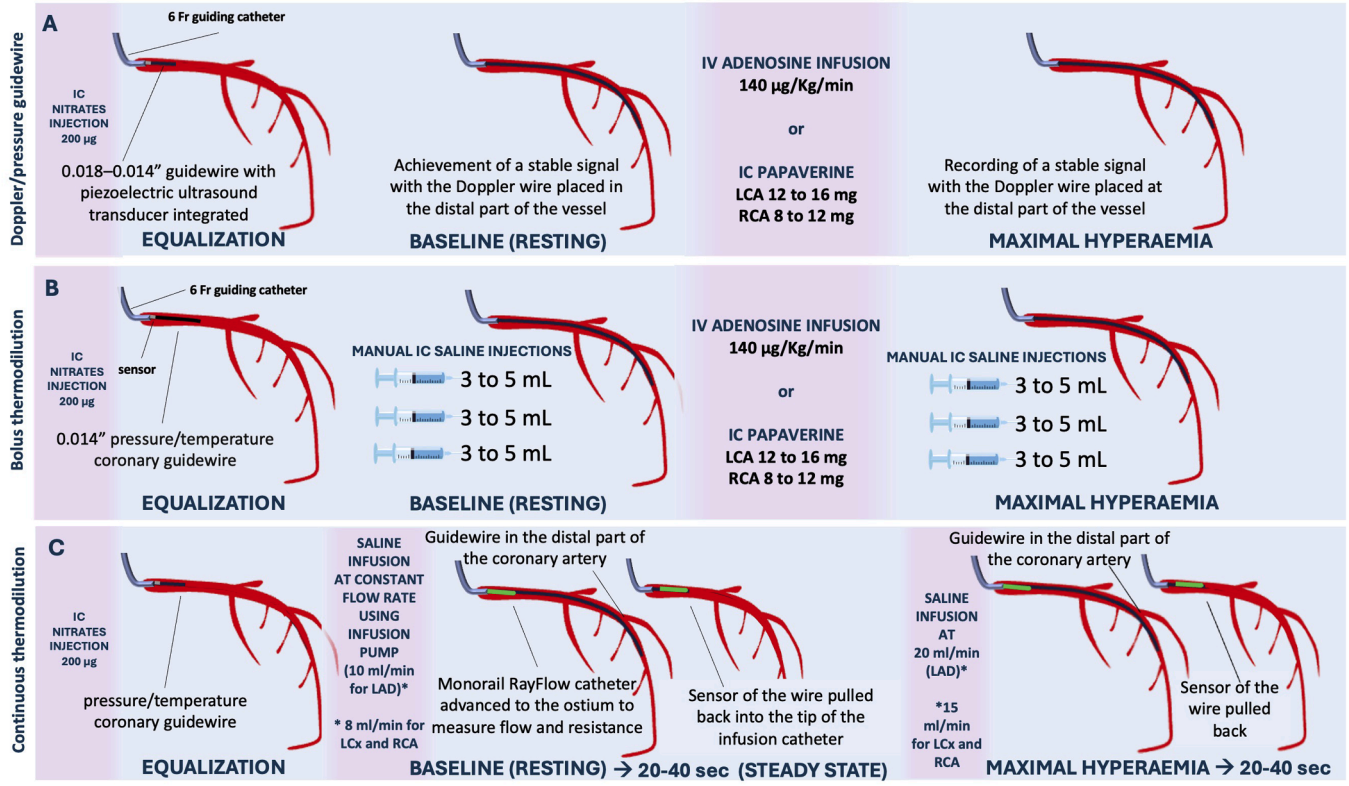


Fig. 2. Procedural steps in invasive coronary vasomotor function testing using combined Doppler/pressure-tipped coronary guidewire (A) and thermodilution method (bolus (B) and continuous (C)).
Abbreviations: Fr, French; IC, intracoronary; µg, micrograms; iv, intravenous; Kg, kilograms; min, minute; LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex; sec, seconds.

Diagnosis of Chest pain display the current status of evidence on the broad availability and accuracy of CMRI for the diagnosis of CMD in stable patients with suspected INOCA, supporting its use in this context with a class IIa recommendation. [42]

Sinha et al. recently investigated the specificity of exercise electrocardiographic stress test in detecting an ischaemic substrate compared against the reference standard of coronary endothelium-independent and endothelium-dependent microvascular function in ANOCA patients. Results showed that ischaemia during electrocardiographic stress test (detected as ECG changes) had 100% specificity and high positive predictive value for detecting CMD. Patients who developed ischaemia during exercise had lower invasive acetylcholine flow reserve (AChFR) values, an index of endothelium-dependent CMD, which was the strongest predictor of ischaemia during exercise. [46] Non-invasive modalities possess significant advantages owing to their less invasive nature and ease of use. However, the integration of non-invasive and invasive testing can provide a comprehensive care in ANOCA/INOCA patients **(Central Illustration)**.

10. Invasive assessment

Invasive coronary vasomotor function testing (CFT) represents the only diagnostic tool able to systematically investigate all INOCA endotypes. [2] A complete CFT includes both vasospasm acetylcholine (ACh) provocation testing and CMD assessment, both necessary to identify the specific INOCA endotype.

The Coronary Vasomotor Disorders International Study (COVADIS) group incorporates two invasive indices in the standardised diagnostic criteria for CMD, requiring either:

- diminished CFR (cut-offs range between $\leq$ 2.0 and $\leq$ 2.5);
- or an abnormal index of coronary microvascular resistance (IMR) > 25. [43]

Two methods are available to invasively test coronary microvascular function: combined Doppler/pressure-tipped coronary guidewires and thermodilution using combined thermistor/pressure-tipped coronary guidewires. The latter can be further performed using bolus or continuous thermodilution (Fig. 2). A complete list of invasive indices with their respective formulae is shown in Table 1.

10.1. Coronary flow reserve

Coronary flow reserve (CFR) assesses the ability of the coronary vasculature to augment coronary blood flow in response to adenosine, and an impaired CFR (<2.5) in the absence of epicardial CAD is hallmark of CMD. [47,48] CFR can be measured using two main modalities (Doppler and thermodilution) and is defined as hyperaemic CBF/resting CBF. When performing bolus thermodilution conjointly with a combined pressure/thermistor guidewire, CFR is obtained as the ratio of mean resting to hyperaemic time (Tmn). [49] Using the Doppler-tipped guidewire, CFR is calculated as the ratio of hyperaemic to resting average peak coronary flow velocity (APV). Compared to PET, Doppler-derived CFR has better agreement and less intraobserver variability than bolus thermodilution-derived CFR. [50] However, despite its superiority compared against bolus thermodilution, there is a learning curve associated with obtaining optimal Doppler signals, which can sometimes limit its use. The continuous thermodilution method is an operator- and hyperaemic agent- independent method that has been validated to directly quantify absolute coronary blood flow (Q) at rest (Q_r) and maximal hyperaemia (Q_h). Continuous thermodilution-derived CFR is significantly lower compared to bolus thermodilution-derived CFR and has three times lower variability. [51] Despite the wealth of

Table 1
Invasive physiological indices of CMD classified according to the three used methods.

	Doppler-derived method	Bolus-thermodilution	Continuous-thermodilution
Pros	Compared with PET, better agreement and less intraobserver variability than bolus thermodilution	Not required vessel rewiring	3-times lower variability compared to bolus-thermodilution
		Ease of obtaining a stable signal	Quantification of true CBF
		Good accuracy in predicting MVO at CMR using bolus thermodilution derived IMR	Not required vasodilator drug
Cons	Vasodilator drug required (adenosine or papaverine) with possible subsequent adverse events	Vasodilator drug required (adenosine or papaverine) with possible subsequent adverse events	Saline infusion velocity switch and vessel rewiring needed (overcome by a new automated version)
	Difficult attainment of a stable signal	CFR overestimation at higher values Low reproducibility (measurements must be repeated 3 times) IMR is influenced by myocardial mass and vessel volume	Q and Rμ dependent on myocardial mass perfused (variability amongst patients)
Indices	**CFR** $= \frac{\text{APV}hyper}{\text{APV}rest}$ **HMR** $= \frac{Pd,hyper}{APV,hyper}$ **mMR** $= \frac{Pd,hyper}{APV,hyper}$* *both measured during the diastolic WF period **MRR** $= \frac{\text{CFR}}{\text{FFR}} x \frac{Pa,rest}{Pa,hyper}$	**CFR** $= \frac{\text{Tmn}rest}{\text{Tmn}hyper}$ **IMR** $=$ Pd $_{hyper}$ x Tmn $_{hyper}$ **RRR** $=$ Tmn $rest\ x \frac{\text{Pd},rest}{\text{IMR}}$ **MRR** $= \frac{\text{CFR}}{\text{FFR}} x \frac{Pa,rest}{Pa,hyper}$	$\boldsymbol{Q} = 1.08\ \frac{Ti}{T} x\ Qi$ $\boldsymbol{R\mu} = \frac{Pd}{Q}$ **CFR** $= \frac{Qhyper}{Qrest}$ $\boldsymbol{MRR} = \frac{\text{True R}\mu,\ rest}{\text{R}\mu,\ hyper}$
Diagnosis	**Structural CMD** **Functional CMD**	↓ CFR - ↑MR ↓ CFR* - Normal or ↓ MR	*CMD identified by impaired CFR was unequivocally associated with ↑ MACE/TVF rates over a 5-year follow-up period, regardless of a pathologically increased MR

Abbreviations: PET, positron emission tomography; CBF, coronary blood flow; CFR, coronary flow reserve; APV, average peak velocity; hyper, hyperaemia; rest, resting; WF, wave-free; HMR, hyperaemic microvascular resistance; mMR, minimal microvascular resistance; MRR, microvascular resistance reserve; IMR, index of microcirculatory resistance; Pd, distal pressure; Tmn, median transit time; RRR, resistance reserve ratio; Pa, aortic pressure; FFR, fractional flow reserve; Q, absolute (true) coronary blood flow; Rμ, absolute microvascular resistance; Ti, temperature of infused saline solution; Qi, saline infusion rate (mL/min); T, difference between body (blood) temperature and temperature of the homogeneous mixture of blood and saline solution (°C); MVO, microvascular obstruction; CMR, cardiac magnetic resonance; MR, microvascular resistance; CMD, coronary microvascular dysfunction.

data linking CFR with mechanistic outcome measures and hard clinical endpoints, it has two main limitations. Firstly, it is not specific to the microvasculature. [52] Secondly, CFR requires measurements at rest, which might be influenced by fluctuations in blood pressure, ventricular contractility, and heart rate, which may lead to lower reproducibility. [53]

10.2. Index of coronary microvascular resistance (IMR)

IMR is calculated as the ratio of the distal coronary pressure (Pd) to the inverse of bolus thermodilution-derived time during maximal hyperaemia, measured with a pressure/temperature wire ($Pd_{hyp} \times Tmn_{hyp}$). Time can vary according to the distance of the thermistor from the arterial ostium. An IMR value >25 is indicative of CMD. [54] In the absence of significant epicardial CAD, IMR has higher reproducibility than CFR. [53]

10.3. Absolute coronary blood flow (Q) and resistance (Rμ)

Bolus-thermodilution and Doppler method have several limitations (Table 1 and Fig. 2), [55,56] leading to the development of the continuous thermodilution method: this enables quantification of true (or absolute) coronary blood flow (Q) and microvascular resistance (Rμ) without the need for a hyperaemic agent (adenosine or papaverine). Maximal hyperaemia is achieved using continuous infusion of saline at room temperature through a monorail catheter advanced over a pressure/temperature sensor-tipped guidewire. [57] A recent study indicates that saline-induced hyperaemia is mediated by haemolysis, leading to local release of endogenous adenosine. [57,58] Q is calculated using the following equation: 1.08 T_i/T x Qi, where Q_i represents the saline flow in the injector (mL/min), T represents the temperature difference between body and the saline-blood mixture at the distal tract of the vessel, T_i represents the temperature difference between body and saline (measured at the location of the saline infusion when the wire is pulled back). [59] Q and Rμ correlate well with absolute flow derived from PET/CT. [50] In INOCA patients undergoing CFT, $Q < 198$ mL/min and Rμ > 416 Woods Units were associated with angina severity. [60] A novel automated method has been validated to overcome some impractical steps, such as guidewire pullbacks and the reprogramming of the infusion pump (Fig. 2). [61]

10.4. Hyperaemic microvascular resistance

The hyperaemic microvascular resistance (HMR) is another microvascular-specific index assessed using a Doppler wire. It is defined as the Pd/ APV ratio during maximal hyperaemia. This formula needs correction for collateral flow in case of obstructive CAD. [62] A study including symptomatic patients with non-obstructive coronary arteries proposed an HMR value $\geq$ 2.5 to identify CMD. Compared to IMR, HMR showed better diagnostic accuracy to detect CMD, predicting both CFR

Table 2
Angiography-derived indices of coronary microvascular resistance.

Index	Formula	Diagnostic and prognostic performance
IMR_{angio}	QFR_{hyp} x Pa_{hyp} x (n $frames_{hyp}$ /frame rate acquisition)	Strong correlation with invasive IMR in both acute and chronic settings $IMR_{angio} > 40$ detects clinically significant CMD (as assessed by IMR and CMRI-based MVO)
NH-IMR_{angio}	Pa_{rest} x QFR_{rest} x (n $frames_{rest}$/frame rate acquisition)	Agreement with invasive IMR only in the acute settings
CaIMR	($Pd_{e\text{-}hyp}$/2.1 x $V_{diastole}$) x L	Reliable prognostic indicator in MINOCA CaIMR $\geq$ 25 demonstrated the highest ROC AUC to predict invasive IMR $\geq$ 25 In chronic settings, CaIMR $\geq$ 25.1 associated with a substantial risk of cardiac mortality or readmission for HF
A-IMR	Parest (L/flow velocity) x [(1.35 x cQFR) – 0.32]	Moderate correlation with IMR in stable CAD No available data in STEMI
Angio-IMR	[Parest – (0.1 x Parest)] x QFR x (L/V_{hyp})	Good correlation with invasive IMR Prognostic role of Angio-IMR > 40 in STEMI patients (↑ risk of cardiac death and hospitalisation for HF)
AccuIMR	Pa x AccuFFR x (L/V)	Slightly better agreement with IMR in CCS than that of STEMI and NSTEMI
AMR	Pa x μQFR/V_{hyp}.	Good correlation and diagnostic accuracy in predicting invasive IMR confirmed in a mixed cohort of ACS and CCS patients

Abbreviations: IMR_{angio}, angiography-derived index of microcirculatory resistance; NH-IMR_{angio}, non-hyperaemic angiography-derived index of microcirculatory resistance; A-IMR, angio-derived index of microcirculatory resistance; AMR, angiographic microvascular resistance; caIMR, coronary angiography-derived index of microvascular resistance; cQFR, contrast quantitative flow ratio; e-hyp, estimated hyperaemic; hyp, hyperaemic; L, vessel length; n frames, number of cine frames required for dye to reach distal landmarks; NH, non-hyperaemic; Pa, mean aortic pressure; Pd, mean distal coronary pressure; QFR, quantitative flow ratio; rest, resting; $V_{diastole}$, mean diastolic flow velocity; V_{hyp}, hyperaemic velocity; μ, Murray's law based; IMR, index of microvascular resistance; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; MVO, microvascular obstruction; MINOCA, myocardial infarction with non-obstructive coronary arteries; HF, heart failure; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; CCS, chronic coronary syndrome; NSTEMI, non ST-segment elevation myocardial infarction; ROC, receiver operating characteristic; AUC, area under the curve.

value (both Doppler and thermodilution-derived) and CMRI-derived myocardial perfusion reserve index. [63] A study of 610 INOCA patients has showed that HMR was a predictor of MACE, and this relationship remained significant after adjusting for age and sex. [64]

10.5. Minimal microvascular resistance

Minimal microvascular resistance (mMR) is another Doppler-based method for coronary microcirculatory resistance assessment and corresponds to the Pd/APV ratio, measured during the diastolic wave-free period and maximal hyperaemia. mMR was introduced to overcome the microcirculatory resistance overestimation by HMR, related to the presence of obstructive CAD, and provides a reliable evaluation of the coronary microcirculation status, regardless of the presence of epicardial CAD. [65] Further evidence on mMR is still required.

10.6. Resistance reserve ratio

Resistance reserve ratio (RRR) is a bolus thermodilution-derived index, defined as the ratio of estimated resting microcirculatory resistance to hyperaemic microcirculatory resistance. Similarly to IMR, the formula for RRR can be modified to account for the presence of epicardial stenosis. The formula for RRR is: $Tmn_{resting}$ x $Pd_{resting}$/IMR. In a study of stable patients with intermediate epicardial stenoses, an RRR < 3.5 was associated with an increased risk of patient-orientated composite outcomes, and a composite of all-cause mortality, myocardial infarction and revascularisation at 5 years despite normal fractional flow reserve (FFR) (> 0.80) and CFR (> 2.0). [66]

10.7. Microvascular resistance reserve

The microvascular resistance reserve (MRR) was introduced to characterise the vasodilator reserve capacity of the coronary microcirculation, considering the influence of concomitant epicardial CAD and the impact of vasodilators on aortic pressure (Pa). [67] MRR theoretically overcomes the limitations of CFR as it is considered specific to the microcirculation. MRR calculation can be applied to all available methods using the following formula: (CFR/FFR) × (Pa_{rest}/Pa_{hyper}), where FFR is the Pd/Pa ratio at maximal hyperaemia. [67] Boerhout et al. evaluated the diagnostic and prognostic performance of MRR derived either from Doppler or bolus thermodilution. Despite both CFR and MRR being independently associated with MACE and target vessel failure (TVF) at 5-year follow-up in vessels with functionally intermediate or non-significant epicardial CAD, only impaired MRR was independently associated with MACE and TVF in case of significant epicardial CAD. [68] MRR variability was approximately two times lower than that of IMR. [51] MRR is independent of myocardial mass and a value of 2.5 has been suggested as the best discriminatory threshold. [69] Nonetheless, the MRR cut-off remains the subject of ongoing investigations. Unlike bolus thermodilution-derived CFR and MRR, measurements derived from Q correlate well with angina severity and quality of life. [70]

10.8. Endothelial function assessment

Unlike adenosine, which acts on VSMC A_{2A} receptors to promote cyclic adenosine monophosphate-mediated vasodilation, ACh acts on endothelial muscarinic receptors, causing cyclic guanosine monophosphate (cGMP)-mediated vasodilation. [71] Endothelial function studies use low-dose intracoronary ACh infusion (either graduated incremental dosing of 10^{-6} to 10^{-4} mol/L or simply 10^{-4} mol/L; 10^{-6} mol/L = 0.18mcg/ml, 10^{-5} mol/L = 1.8mcg/ml and 10^{-4} mol/L = 18mcg/ml) over 2–3 min. In this protocol, increase in flow more than 50 % compared to baseline indicates normal endothelium-dependent vasodilation, whereas no change or reduction in flow implicates impairment. [72] Reports showed that in INOCA patients, myocardial ischaemia, either during exercise stress myocardial perfusion scintigraphy or at rest, correlated with coronary endothelial dysfunction assessed by intracoronary ACh test. [72,73] Consistent with these results, AChFR - a marker of coronary endothelial function - has been reported as the strongest predictor of ischaemic ECG changes during exercise electrocardiographic stress test. [46] Volumetric flow estimation from Doppler flow velocity also incorporates vessel diameter. Since ACh can cause either epicardial vasodilation or vasoconstriction, CBF should be calculated using quantitative coronary angiography (QCA) to estimate epicardial diameter as follows: 0.5xπ(APV) (diameter/2) [2]. AChFR is obtained as CBF_{ACh}/CBF_{rest}. A value ≤ 1.5 is suggestive of coronary endothelial dysfunction and associated with adverse cardiovascular events. [74] Some centres also separately characterise epicardial endothelial dysfunction as <20 % increase in vessel calibre (using QCA) in response to ACh infusion. [17]

Table 3
Recommended pharmacological treatments in CMD patients.

Drug class	Effects	Drug Dosage
BBs	↓ Myocardial O_2 demand ↓ Myocardial contractility ↓ Resting CBF Antioxidant properties ↑ NO-mediated vasodilation	Carvedilol (unselective blocker of α_1- and β_1/β_2-adrenceptors) 12.5 mg/daily titrated up to 50 mg once/twice daily Nebivolol (selective β_1-adrenergic receptor antagonist) 2.5 – 10 mg daily
ACEi	↑ CFR ↑ Myocardial O_2 supply ↓ Workload ↓ Angina Improvement of vascular remodelling	Enalapril 10 mg daily Quinapril 20 mg daily (up to 40 mg) Ramipril 2.5–10mg
CCBs	↓ Microvascular tone ↓ Myocardial O_2 consumption	Non-dihydropyridine (e.g., verapamil 40 mg BID titrated) as second line therapy when BBs are not tolerated or ineffective Dihydropyridine (e.g., amlodipine up to 10 mg daily) as third line therapy in addition to BBs In case of concomitant demonstrated VSA, dosages much higher are recommended (e.g., diltiazem up to 400 mg daily), or a combination of both dihydropyridine and non-dihydropyridine CCBs
Statins	Improvement of coronary endothelial function ↓ Vascular Inflammation by OS reduction	Pravastatin Simvastatin Rosuvastatin up to 40 mg daily (according to patient LDL cholesterol target) Atorvastatin up to 80 mg daily (according to patient LDL cholesterol target)
Nicorandil	↑ CBF ↑ Microvascular dilation ↓ Cardiac load ↓ Oxidative injury	Nicorandil (up to 10–20 mg twice daily)
Ranolazine	↑ Intraventricular relaxation ↑ Myocardial perfusion ↓ Anginal symptoms	Ranolazine 375 – 750 mg twice daily (up to 1 g twice daily in the US)
Ivabradine	↑ Myocardial perfusion ↓ Anginal symptoms	Ivabradine 5 mg twice daily
Trimetazidine	↑ Glucose utilization by selective inhibition of fatty acid metabolism ↑ Exercise time before angina onset and number of angina-free patients	Trimetazidine 35 mg twice daily

Abbreviations: BBs, beta-blockers; O_2, oxygen; CBF, coronary blood flow; NO, nitric oxide; mg, milligrams; CFR, coronary flow reserve; ACEi, angiotensin converter enzyme inhibitors; calcium channel blockers, CCBs; OS, oxidative stress; US, United States; LDL, low density lipoprotein.

10.9. Intracoronary electrocardiogram

Invasive measurements, such as CFR and MRR, detect patients with an ischaemic substrate and do not assess for the presence of myocardial ischaemia itself (i.e., these are sensitive markers). Intracoronary electrocardiogram (icECG), on the other hand, is purported to demonstrate actual ischaemia during an invasive study. It has, therefore, been identified as a potential tool to diagnose CMD with high specificity in the catheter laboratory. In a recent proof-of-concept trial, INOCA patients were studied with simultaneously obtained invasive coronary physiological indices and icECG parameters, which successfully classified vessel-specific CMD and detected actual reversible ischaemia in the CMD-related territory. Ischaemia was demonstrated only in half of the vessels with an impaired CMD and was proven to be heterogeneously distributed. [75]

11. Angiography-derived assessment

To overcome limitations concerning the conventional sensor wire-derived indices, coronary angiography-derived indices of microcirculatory resistance have recently emerged to assess coronary microcirculation without requiring adenosine administration (Table 2). These techniques rely on angiographic analyses for extrapolating coronary flow velocity or the time, while deriving Pd using computational fluid dynamics or contrast quantitative flow reserve (cQFR). Many have been evaluated in the context of obstructive CAD and further studies are warranted to evaluate their utility in patients with non-obstructive coronary arteries.

11.1. Angiography-derived index of microcirculatory resistance

The angiography-derived index of microcirculatory resistance (IMR_{angio}) was developed using QFR (Medis). [76] IMR_{angio} was demonstrated to have a strong correlation with IMR in the infarct-related artery and non-culprit vessels of ST-elevation myocardial infarction (STEMI) patients (both pre- and post-PCI). $IMR_{angio} > 40$ was able to detect clinically significant CMD, as assessed by IMR and CMRI-based microvascular obstruction. [76] A significant correlation of IMR_{angio} with IMR has been also confirmed in non-ST elevation myocardial infarction (NSTEMI) and chronic coronary syndrome (CCS) patients. [77]

11.2. Non-hyperaemic angiography-derived index of microcirculatory resistance

A non-hyperaemic version of IMR_{angio} (NH-IMR_{angio}) demonstrated good accuracy in predicting CMD in the infarct-related artery of STEMI compared with IMR and CMRI-derived microvascular obstruction. [77] In acute settings, the vasodilatory response of the infarct-related artery to hyperaemic stimuli is blunted, and a minimal difference is registered between basal and hyperaemic resistance. Therefore, the agreement between NH-IMR_{angio} and invasive IMR is maintained. Conversely, when the vasodilatory reserve is normal, vascular tone significantly changes during maximal hyperaemia. Here, NH-IMR_{angio} does not reflect the minimal level of resistance achievable at maximal hyperaemia. [77]

11.3. Coronary angiography-derived index of microvascular resistance

The coronary angiography-derived index of microvascular resistance (caIMR) is calculated as the product of HMR (obtained from computational fluid dynamics simulations) and a constant (L) corresponding to the vessel length. [78] CaIMR is a reliable prognostic indicator in myocardial infarction with non-obstructive coronary arteries. A value $\geq$ 25 demonstrated the highest receiver-operating characteristic area

under the curve to predict invasive IMR ≥ 25. In chronic settings, CaIMR ≥ 25.1 was significantly associated with a substantial risk of cardiac mortality or readmission for heart failure at a median follow-up of 28 months post-PCI. [79]

11.4. Other angiography-derived indices

For completeness, other functional angiography-derived indices are reported below. The angio-based index of microcirculatory resistance (A-IMR) was validated in 44 patients with CCS and an intermediate left anterior descending (LAD) artery lesion, showing good correlation with invasive IMR. [80] Similarly, the index Angio-IMR correlated well with invasive IMR. Two cohorts of STEMI patients followed up for 10 years confirmed its prognostic role, in which the subgroup with angio-IMR > 40 had a significantly increased risk of cardiac death and hospitalisation for heart failure. [81]

AccuIMR was computed using a software based on acquiring two angiographic projections, 3-dimensional vessel reconstruction, and TIMI frame count analysis. AccuIMR diagnostic performance maintained a high level in patients with STEMI, NSTEMI, and CCS. Notably, AccuIMR showed slightly better agreement with IMR in CCS than that of STEMI and NSTEMI. [82] Finally, the angio-derived microcirculatory resistance (AMR) index is based on the single angiographic view μQFR analysis. The coronary contour is automatically outlined, whilst contrast flow velocity is derived from the length of the centre line divided by the contrast filling time. AMR demonstrated good correlation and diagnostic accuracy in predicting invasive IMR in a mixed cohort of ACS and CCS patients. [83]

12. Therapeutic options

Despite ongoing improvements in CMD diagnostic approaches, sufficient data regarding appropriate treatments is lacking. [84] A consistent proportion of patients report persistent symptoms and poor quality of life despite treatment. [85] In the Coronary Microvascular Angina (CorMicA) trial, patient-tailored medical treatment, guided by invasive CFT, improved anginal symptoms up to 1-year follow-up. [86] Furthermore, the Characterising Mechanisms in Patients with Coronary Microvascular Disease to Stratify Therapy (ChaMP-CMD) trial recently reported the clinical relevance of measuring CFR in the catheter laboratory as, in an otherwise phenotypically identical patient cohort with limiting ANOCA, only those with an impaired CFR derived objective benefit from anti-ischaemic therapy. Based on the recent findings, the latest 2024 ACC/AHA guidelines on the management of chronic coronary disease provide specific recommendations for each INOCA endotype, underscoring the need to address the precise underlying mechanism and proposing a multi-step approach in case of persistent symptoms. [87] Medications are commonly used in combination and the dosages are adjusted based on patient's response and tolerance (Table 3). A patient-centred multidisciplinary approach is essential to monitoring and managing INOCA symptoms. Communication amongst the health care professionals and the patient is essential to improve outcomes and quality of life. Nursing care of the patients hospitalised with heart failure is pivotal and include monitoring of symptoms and fluid intake/output, supporting with activities of daily living, and patient education. [88]

12.1. Lifestyle and risk factors control

Fundamental to CMD prevention and treatment are lifestyle management and controlling cardiovascular risk factors. Moreover, psychosocial factors may play a crucial role in abnormal vascular reactivity and symptoms. The greater coronary reactivity to cold pressor test observed in women with INOCA may reflect non-endothelial dependent mechanisms secondary to sympathetic stress. [89] Psychological counselling may help to cope with stress, thus improving anginal symptoms. Moderate physical activity (2–3 times/week) appears to improve physical functioning over 8 weeks and reduce pain severity. [90] Women with chest pain and normal coronaries undergoing cardiac rehabilitation exercise programs reported significant amelioration in symptom severity, Hospital Anxiety and Depression Scale scores and general health. [91] In hypertensive INOCA patients, lowering blood pressure is necessary to improve CFR. [92] An inverse correlation was observed between PET-derived CFR and total lipid levels, including low-density lipoprotein cholesterol. [93] Similar endothelium-dependent and independent vasodilator dysfunction has been demonstrated in both type 1 and 2 diabetes mellitus patients, proposing chronic hyperglycaemia involvement in CMD. [94]

12.2. Aspirin

Aspirin should be considered in all patients with CMD as part of the baseline therapy, in association with angiotensin-converting enzyme inhibitors (ACEi) and statins. [87] Low doses (≤100 mg daily) could prevent adverse outcomes by blocking thromboxane A2, a vasoconstrictor, and reducing endothelial platelet adhesion. Aspirin and $P2Y_{12}$ platelet inhibitors minimise formation of platelet-rich microemboli, protecting microcirculation from oxidative damage. [95]

12.3. Angiotensin-converting enzyme inhibitors

Amongst antihypertensives, ACEi, or alternative angiotensin receptor blockers, should be considered for patients with established CMD, as these improve vascular remodelling, CFR, and reduce anginal symptoms. [96] Enalapril (10 mg/day) is demonstrated to reduce exercise-induced ischaemia in patients with CMD, probably via direct modulation of coronary microvascular tone. [97] Quinapril administration in women with CMD has been associated with significant CFR improvements at invasive testing, as well as angina symptom frequency, at a 16-week follow-up. [96]

In hypertensive patients, benefits of 12-month therapy with perindopril (4 to 8 mg) in structural repair of coronary arterioles, comprising regression of periarteriolar fibrosis at biopsy and improvement in coronary reserve, were demonstrated. [98] However, a 6-month perindopril treatment in hypertrophic cardiomyopathy patients with CMD was not associated with significant improvement in myocardial blood flow (MBF). A significant improvement was observed in patients without myocardial fibrosis, suggesting potential utility in early stages. [99]

12.4. Beta-blockers

For patients with an established diagnosis of CMD, an initial therapy with beta-blockers (BBs) should be considered. [2,47] BBs decrease myocardial oxygen demand by reducing myocardial contractility and work. Third generation BBs, such as carvedilol and nebivolol, may enhance CBF by their ability to promote NO-mediated vasodilation. [100] Particularly, carvedilol 6.25 mg BID is recommended in patients with MVA, with the possibility of uptitration. [87] Complete invasive assessment has practical utility in ANOCA/INOCA patients as a means of personalizing therapies, and in case of concomitant VSA, BBs prescription should be avoided. [2] Indeed, BBs without $alpha_1$-adrenergic antagonist activity may exacerbate epicardial spasm attacks through the antagonism of $beta_2$-adrenergic receptors. BBs are therefore best avoided in VSA and, if indicated, BBs with mixed $alpha_1$ and beta-adrenergic activity should be considered (i.e. carvedilol or labetalol).

12.5. Calcium channel blockers

Calcium-channel blockers (CCBs) are effective in decreasing microvascular tone and relieving spasm, although evidence of their effect on CBF is limited. [2] Non-dihydropyridine CCBs (e.g., verapamil 40 mg BID titrated) constitute the second line therapy in CMD patients when

BBs are not tolerated or ineffective, whereas dihydropyridine CCBs (e.g., amlodipine) can be prescribed as third line therapy in addition to BBs. [87] In case of concomitant demonstrated VSA, dosages much higher than those used to treat obstructive CAD (e.g., diltiazem up to 400 mg daily), or a combination of both dihydropyridine and non-dihydropyridine CCBs, are recommended. In CMD patients treated with nifedipine and verapamil for 1 month, exercise stress test parameters and symptoms improved, compared with placebo. [101] The recent ChaMP-CMD trial randomised 87 ANOCA patients to receive 4 week-therapy of amlodipine or ranolazine after undergoing blinded invasive CFT. After a 1-week washout, patients crossed over to the other drug for 4 weeks and underwent exercise treadmill test after each treatment cycle. The CMD group (CFR $<$ 2.5) showed a significantly greater increment in exercise time compared with the reference group (CFR $\geq$ 2.5) in response to both drugs. However, a greater increment in Seattle Angina Questionnaire (SAQ) summary score was reported in CMD group compared to the reference group in response to ranolazine, but not to amlodipine. The loss in function after cessation of therapy in the CMD group suggests a causal connection between the pathophysiological classification and response to therapy. This demonstrates the association between CFR and an improvement in exercise capacity in response to anti-ischaemic therapy. [102] In a systematic review carried out by Marinescu et al., only a case-control study provided evidence for CCB utilisation, failing to show an effect of diltiazem on CFR. [103] The Efficacy of Diltiazem to Improve Coronary Microvascular Dysfunction (EDIT-CMD) trial findings reported that diltiazem, compared with placebo, did not improve CMD. Specifically, patients on placebo showed an increase in CFR, whereas patients on diltiazem showed a decrease over 6 weeks, suggesting an improvement in the placebo group. [104] However, the study was not powered on the effect of diltiazem on individual endotypes of coronary vasomotor dysfunction.

12.6. Statins

Beyond their lipid-lowering effects, statins are recommended for their beneficial effect on endothelial function. [105] Small randomised studies have shown beneficial effects regarding prolongation of exercise duration in CMD patients taking pravastatin or simvastatin compared to placebo. [106] Six months of treatment with atorvastatin plus ramipril improved endothelial function (measured by endothelium-mediated dilation) and quality of life (measured by exercise ability and symptoms of daily life) in CMD patients. Benefits of these drugs may be related to oxidative stress reduction. [107]

12.7. Nicorandil

Nicorandil has dual properties of a nitrate and ATP-sensitive K^+ channel agonist. Vasodilation stems from NO synthesis and hyperpolarisation across VSMC membranes, leading to reduced opening of voltage-gated Ca^{2+} channels. [108] Nicorandil can improve CBF by activating the cGMP signalling pathway in VSMCs to dilate blood vessels, decreasing cardiac load and coronary flow resistance. As a third line option, long-term treatment (5 mg BID, uptitrated) may result in cardiovascular protection through pleiotropic effects, including reductions in oxidative injury and systemic inflammation. [87,109] In CMD patients experiencing refractory symptoms, nicorandil use is recommended on top of BBs and CCBs. [2] A mild dose-dependant baroceptor reflex tachycardia can occur.

12.8. Ranolazine

Ranolazine is a late sodium channel blocker that reduces intracellular Ca^{2+}, improving intraventricular relaxation and myocardial perfusion and reducing myocardial oxygen consumption. It does not alter blood pressure or heart rate, thus can safely be combined with other therapies (dosage 375 mg BID, uptitrated). A recent randomised trial showed that ranolazine improves symptoms and exercise capacity in patients with CFR $<$ 2.5. [102] Myocardial ischaemia may also improve, particularly amongst women with low CFR, [2] as well as CFR and IMR indices. [110] Villano et al. randomised 46 patients with CMD and inadequately controlled symptoms by standard anti-ischaemic therapy to ivabradine (5 mg twice/day), ranolazine (375 mg twice/-day), or placebo for 4 weeks. Both drugs significantly improved SAQ and Euro Quality of Life (EuroQoL) scores compared with placebo; ranolazine showed greater effects on some SAQ categories and EuroQoL scales. Time to 1-mm ST-segment depression and exercise duration were improved by ranolazine compared with placebo. [111]

12.9. Ivabradine

CMD patients reporting persistent symptoms may benefit from ivabradine, a selective pacemaker current blocker for sinoatrial node. This decreases heart rate both at rest and during exercise, without affecting left ventricular contractility. [2,111] However, its efficacy in CMD is poorly investigated and still controversial. Symptomatic improvement was demonstrated in patients taking ivabradine, without any changes in microvascular function indices. [111]

12.10. Trimetazidine

Trimetazidine is an anti-ischaemic metabolic agent that improves myocardial glucose utilisation by inhibiting fatty acids metabolism. Trimetazidine exerts no effect on coronary flow, contractility, blood pressure, or heart rate. Therefore, it can be combined with conventional pharmacotherapy for CAD. A randomised trial conducted in patients with coronary 'slow flow' phenomenon showed that trimetazidine (20 mg three times/day) improved endothelial products such as ET-1 and NO as well as anginal symptoms in patients at 4 weeks, compared to placebo. [112] The latest CCS guidelines and the European Consensus document on INOCA recommend trimetazidine as a second-line drug in patients whose symptoms are not adequately controlled by, or who are intolerant to, other antianginal medicines. [2,47]

12.11. Tricyclic antidepressants

Enhanced pain perception may exacerbate anginal symptoms refractory to conventional therapies. Low-dose tricyclic antidepressants may reduce symptom intensity due to their effect on several conditions causing chronic pain. In a randomised trial conducted on 18 women with chest pain and non-obstructive coronary arteries, imipramine (50 mg/day) reduced chest pain incidence compared with placebo. Failure to demonstrate improvements in quality of life could be attributable to the high occurrence of side effects (dry mouth and dizziness). [113]

13. Non-pharmacological treatments

13.1. Neuromodulation

Neuromodulation is the variation of nerve activity through targeted stimuli. Spinal cord stimulation (invasive) or transcutaneous electrical nerve stimulation (TENS) (non-invasive) may be helpful for angina unresponsive to optimal medical therapy. A small trial found that PET-derived coronary resistance had a trend towards reduction in patients undergoing TENS. [114] In a randomised trial involving patients with refractory MVA, spinal cord stimulation was associated with improvements in angina and ST-segment depression on both ambulatory monitoring and dobutamine stress echocardiography. [115] Further research is expected to weigh benefits and risks regarding the implantation of an invasive device.

13.2. Enhanced external counterpulsation

Enhanced external counterpulsation (EECP) is a non-invasive medical device recommended (class IIb) in patients with anginal symptoms refractory to optimal medical therapy or revascularisation. However, its use remains limited due to costs, noise, and discomfort caused by vibration and compression. A mobile, motorised EECP was introduced to address these limitations, with improvement of functional class, coronary perfusion, and cardiac output. [116] A randomised trial including 83 patients demonstrated significant CFR improvement in subjects undergoing 4-week EECP program compared to controls. [117]

13.3. Coronary sinus reducer

The Coronary Sinus Reducer is an hour-glass shaped stent designed for percutaneous implantation in the coronary sinus to increase proximal coronary venous pressure, thereby redistributing MBF to underperfused myocardium. The INROAD study investigated the effect of the coronary sinus reducer on CMD in patients reporting anginal symptoms, despite optimised revascularisation and up-titrated anti-anginal drugs. Reducer implantation was associated with significant improvement in coronary microvascular function, shown by a decrease in IMR and increase in CFR and RRR, 4 months post-implantation. Anginal symptoms improved in 76.1 % of patients, and SAQ score increased of around 3 points. These findings expand evidence from previous proof-of-concept studies. [118] The ongoing randomised double-blinded REducing Microvascular Dysfunction in Patients With Angina, Ischaemia and unobstructED coronary Arteries (REMEDY) study will investigate the effects of coronary sinus reducer on symptoms and myocardial perfusion in ANOCA patients at 6 months after implantation.

14. Future directions

14.1. Endothelin receptor antagonists

Higher levels of ET-1 are associated with doubled risk of CMD. Endothelin receptor antagonists (ERA) have been shown to improve microvascular endothelial dysfunction in patients with CMD. [119] Clinical trials assessing the impact of ERA on patient symptoms have produced heterogenous results. Zibotentan is an ERA that specifically blocks the ET-A receptor which mediates vasoconstriction and not the counter-regulatory vasodilating ET-B receptor. The larger randomised, double-blind, placebo-controlled, sequential crossover Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial compared the impact of zibotentan (10 mg daily) versus placebo on treadmill exercise time in 118 patients with MVA After 12-week treatment, no significant difference in the primary endpoint (exercise duration) was found ($P = 0.587$). However, zibotentan increased plasma ET-1 levels, and global myocardial blood flow, while significantly lowering haemoglobin level, systolic and diastolic blood pressure ($p < 0.001$). Adverse events secondary to fluid retention were higher during the zibotentan period (60.2 %) compared to placebo (14.4 %, $p < 0.001$). [120] Further studies will be required to explore long-term treatment with lower zibotentan doses in combination with agents able to attenuate fluid retention.

14.2. Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors inhibit cGMP degradation, causing increased cGMP levels and VSMC relaxation. In female INOCA patients with CFR $\leq$ 2.5, sildenafil was demonstrated to improve CFR and anginal symptoms. The degree of improvement was related to the severity of impaired baseline dysfunction: a greater improvement was observed in patients with a worse baseline CMD. For women with baseline CFR $>$ 2.5, the value remained unchanged. [121] The efficacy in CMD remains to be confirmed in larger-scale studies.

14.3. Cell and gene-based therapies

CD34 stem cell therapy promotes angiogenesis and microcirculation recovery. [122] Based on these encouraging results, therapy using autologous CD34 cells for treating CMD deserves further investigation. In a single-arm, prospective study, 20 patients with INOCA and coronary endothelial dysfunction followed a protocol including leukapheresis and infusion of CD34 cells into the LAD artery. At 6 months, cell therapy was associated with improvements in coronary microvascular function, SAQ score, and reduced nitroglycerine use. [123]

14.4. Sodium-glucose cotransporter 2 inhibitors

Beneficial cardiovascular effects of sodium-glucose cotransporter 2 inhibitors, regardless of diabetes mellitus presence, are well known. A phase III study showed that 4-week treatment with dapagliflozin increased myocardial flow reserve and reduced resting MBF, measured by PET, in patients with type 2 diabetes. [124] These effects might be partly due to the action on the endothelium. [125] Moreover, the reduction of excess glucose in the myocardium may lower inflammation. However, the impacts on CMD needs further research.

15. Conclusion

CMD encompasses structural and functional abnormalities of the coronary microcirculation responsible for myocardial ischaemia. Despite the considerable number of non-invasive and invasive tools to establish a correct diagnosis and prognostic stratification, there remains a lack of research surrounding the potential efficacy of emerging therapeutic strategies and their applicability to CMD. INOCA endotypes are often not properly investigated and, as a result, patients do not receive tailored therapy, thus experiencing recurrent symptoms. There is an urgent need to address the physical and psychosocial needs of these patients, a concept already introduced through various patient support groups. The purpose is to raise awareness amongst patients and physicians by sharing real-life experiences and knowledge. It is necessary for doctors to establish a correct diagnosis using the most appropriate tool to ensure INOCA patients receive optimal care.

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Declaration of competing interest

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