Management of ischaemia with non-obstructive coronary arteries (INOCA)

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ABSTRACT

Up to half of patients undergoing elective coronary angiography for the investigation of chest pain do not present with evidence of obstructive coronary artery disease. These patients are often discharged with a diagnosis of non-cardiac chest pain, yet many could have an ischaemic basis for their symptoms. This type of ischaemic chest pain in the absence of obstructive coronary artery disease is referred to as INOCA (ischaemia with non-obstructive coronary arteries). This comprehensive review of INOCA management looks at why these patients require treatment, who requires treatment based on diagnostic evaluation, what clinical treatment targets should be considered, how to treat patients using a personalised medicine approach, when to initiate treatment, and where future research is progressing.

Introduction

Patients with symptoms and signs suggestive of ischaemic heart disease but found to have no obstructive coronary arteries on angiography (that is, no coronary lesions on angiography $\geq 50\%$) should be diagnosed with INOCA (ischaemia with non-obstructive coronary arteries).¹ However, these symptoms are often dismissed as non-cardiac chest pain, and patients are given no explanation to account for their symptoms or no targeted treatment to alleviate their pain. Building on the previous literature, this comprehensive review provides a holistic approach to the management of INOCA by looking at why these patients require treatment, who requires treatment based upon diagnostic evaluation, what clinical treatment targets should be considered, how to treat patients using a personalised medicine approach, when to initiate treatment, and where future research is progressing (summarised in fig 1).

Sources and selection criteria

A literature search of PubMed and Embase databases for studies published between January 1980 and December 2020 in the English language was undertaken for the health risks associated with INOCA, original papers characterising the various clinical forms of INOCA, clinical studies defining the pathophysiological mechanisms of INOCA, and clinical trials evaluating the efficacy of treatments. In assessing the health risks associated with INOCA, we searched PubMed for prognostic studies using the following terms: “vasospastic angina,” “variant angina,” “Prinzmetal angina,” “syndrome X,” “microvascular angina,” “coronary slow flow phenomenon,” “microvascular spasm,” “INOCA,” “angina” or “chest pain” and “normal coronary arteries,” “non-obstructive coronary artery disease,”

or “normal angiography.” These terms were also used to identify the original papers where the clinical entities were created. The pathophysiological mechanisms responsible for INOCA were determined from review papers, with reference back to the original studies. Finally, the therapeutic clinical trials were identified by a search of PubMed and Embase from January 1980 to December 2020 with the following keywords: “angina” or “chest pain” and “normal coronary arteries,” “non-obstructive coronary artery disease,” or “normal angiography.” This review was supplemented by the authors’ own personal reference collections. Only clinical trials that investigated the impact of treatments on patient symptoms or adverse events were included in this report. Eligible studies were included if they were published between January 1980 and December 2020; in the English language; able to quantitate outcome from treatment, reported as either related to patient symptoms/functioning or clinical events.

In addition to providing data supporting the rationale for treating patients with INOCA, this review provides a pragmatic, holistic, patient focused strategy for managing these patients. The review includes diagnostic considerations to identify the underlying mechanisms and therefore appropriate treatment targets, as well as suggestions for when treatment should be initiated. These suggestions are based on previous publications and discussions during professional society conferences.

Epidemiology

The prevalence of INOCA is difficult to quantitate because of the limited population datasets that have documented the presence of myocardial ischaemia in the absence of obstructive coronary artery disease. However, a comprehensive US dataset of almost

Fig 1 | Synopsis of clinical approaches for INOCA treatment

400 000 patients undergoing elective coronary angiography reported that 59% had no evidence of obstructive coronary artery disease.² Although we do not know how many patients completely fulfilled the criteria for INOCA, the data suggest that more than half undergoing elective angiography could have INOCA. Moreover, smaller selective studies of INOCA have reported an increased risk of major adverse cardiovascular events (MACE),³ threefold to fourfold increased risk of hospital admission,⁴ and hence a high healthcare cost burden⁵ in these patients.

Why treat?

The treatment of cardiovascular disorders aims to prevent MACE or reduce symptoms to improve quality of life (that is, improve health outcomes or status). Thus, in order to justify the treatment of patients with INOCA, health professionals should understand the impact of the disorder on MACE and health status.

Increased risk of MACE

Prognostic studies of patients with INOCA have reported heterogeneous outcomes owing to different recruitment strategies, with some including an unselected patient cohort and others using more selective criteria such as documented ischaemia, coronary microvascular dysfunction, or vasospastic angina. Considering these limitations, a comprehensive meta-analysis reported an overall estimated incidence of MACE (all cause mortality and myocardial infarction) of 0.98 per 100 person years, which is less favourable than the 0.2 per 100 person years reported in a similarly aged general population in North America.³

Prospectively conducted international registries of vasospastic angina and microvascular angina have also provided insights into the incidence of MACE in patients with INOCA. A prospective, comprehensive, vasospastic angina registry in Japan showed a 6% frequency of MACE,⁶ with a subsequent extension study reporting that this proportion was slightly lower in Japanese patients than in white patients.⁷ Furthermore, a recent international registry of microvascular angina reported an annual MACE incidence of 7.7% per patient year, but found no ethnic differences in this outcome.⁸ Hence patients with INOCA have an under-appreciated risk of MACE and therefore warrant treatments to reduce MACE; however, no large prospective randomised clinical trials have been published that evaluate the benefit of cardioprotective treatments in these patients.

Impaired health status

Patients with chronic stable angina (irrespective of the presence or absence of obstructive coronary arteries) will have an impaired health status, where health status is defined as the impact of a disease on patient function as reported by the patient.⁹ This status includes the impact of angina symptoms, which produce functional limitations (eg, reduce exercise capacity), and how they affect quality of life (fig 2).¹⁰ Thus, reducing angina symptoms would

be expected to improve physical functioning and quality of life.

An estimated 50% of patients with stable chest pain and normal angiography will experience recurrent episodes of chest pain,^{11 12} which is a similar rate to those with obstructive coronary artery disease.¹² Furthermore, about 15-25% of these patients are readmitted with chest pain or undergo repeat angiography (or both), thereby also affecting health resources.⁴ Moreover, compared with healthy controls, patients with chest pain and non-obstructive coronary arteries have a reduced quality of life at 12 months.¹²

Thus, patients with INOCA have both a small increased risk of MACE and significantly impaired health status, thereby underscoring the importance of considering both cardioprotective treatments to reduce MACE and anti-anginal treatments to improve symptoms and health status.

Who to treat?

The decision on who to treat is based on two fundamental diagnostic considerations: (1) is the chest pain or presenting symptom ischaemic in nature (that is, INOCA), and (2) what is the underlying pathophysiological mechanisms responsible for the ischaemic symptom (fig 1)? Answering these questions will identify a cohort of patients with INOCA who could benefit from pathophysiologically targeted treatments.

INOCA is common, is under-diagnosed, requires careful assessment to exclude non-ischaemic causes, and often needs functional coronary angiography to identify the underlying vasomotor pathophysiological mechanism responsible for the chest pain. Although macrovascular coronary spasm (vasospastic angina) is well accepted because it can be visualised on angiography, coronary microvascular disorders remain more elusive owing to multiple potential mechanisms.

Identification of INOCA in patients

Owing to the existence of multiple causes of chest pain, diagnostic evaluation of patients with chest pain and non-obstructive coronary arteries requires excluding non-cardiac and non-ischaemic causes, and obtaining clinical evidence implicating the presence of myocardial ischaemia.

Figure 3 summarises common non-cardiac and non-ischaemic causes of chest pain in the absence of obstructive coronary arteries on angiography. These causes can often be delineated with a comprehensive clinical history but might need additional investigations such as endoscopy, oesophageal manometry, biliary ultrasonography, and echocardiography. Ideally, these causes should have been excluded before invasive angiography, thereby avoiding this invasive procedure. Moreover, these disorders should be excluded before embarking on cardiac treatments, although occasionally a trial of anti-anginal treatment might be warranted when the underlying cause remains unclear.

Fig 2 | Overview of health status domains in coronary artery disease. Adapted with permission from Spertus (2008)¹⁰

After excluding non-cardiac or non-ischaemic causes of the chest pain, evidence of myocardial ischaemia should be ascertained to make the diagnosis of INOCA. The term “myocardial ischaemia” describes an inadequate coronary blood flow to supply the myocardium’s metabolic demand, so that myocardial cells become hypoxic and accumulate lactic acid. This pathophysiological concept requires the measurement of biochemical markers, but these are seldom measured in routine clinical practice. Thus, clinical surrogates are used as markers of myocardial ischaemia including:

- Typical angina pectoris that might occur with exertion, stress, or at rest (that is, a strangling sensation in the chest—from the Greek word “ankhōnē” and Latin word “pectoris”)
- Ischaemic ECG (electrocardiogram) changes

- Impaired myocardial perfusion on stress imaging
- Stress induced regional wall motion abnormality
- Abnormal hyperaemic coronary blood flow responses (that is, impaired coronary flow reserve).

When one of these markers is documented, the patient is considered as having ischaemic chest pain, and thus a diagnosis of INOCA would be considered in the absence of obstructive coronary artery disease (that is, no coronary lesions $\geq 50\%$ on angiography).

Pathophysiological mechanisms responsible for INOCA

The potential pathophysiological mechanisms responsible for myocardial ischaemia could include an impaired coronary blood flow (epicardial coronary artery spasm or coronary microvascular dysfunction)

Fig 3 | Common causes of chest pain in patients with non-obstructive coronary arteries. INOCA=ischæmia with non-obstructive coronary arteries

or increased myocardial oxygen demand (that is, tachycardia or myocardial workload). These mechanisms might be evident during the clinical presentation, for example, a spontaneous episode of coronary artery spasm during diagnostic angiography or a tachyarrhythmia at 170 beats per minute during chest pain. However, often the underlying mechanism is not evident on initial evaluation and further assessment beyond conventional invasive structural coronary angiography is required.

Use of functional coronary angiography to identify underlying mechanisms

In structural coronary angiography, the luminal coronary anatomy is imaged, and the presence of obstructive coronary artery disease (usually due to atherosclerotic disease) evaluated as a cause of the chest pain. In functional coronary angiography, pathophysiological assessment of the coronary circulation is undertaken to assess:

- Whether equivocal coronary stenoses are functionally obstructive, via measurement of fractional flow reserve
- Whether coronary microvascular dysfunction is present by evaluation of coronary flow reserve (CFR), microvascular resistance measures (index of microvascular resistance or hyperaemic microvascular resistance), or the presence of the angiographic coronary slow flow phenomenon
- Whether inducible coronary artery spasm is present on provocative spasm testing with intracoronary acetylcholine.

Although functional coronary angiography identifies key potential pathophysiological mechanisms responsible for ischaemic chest pain in INOCA, it is rarely conducted in the large cohort of patients with unexplained chest pain and non-obstructive coronary arteries.

The CorMICA trial randomised 151 patients with angina and non-obstructive coronary artery disease to either functional angiography with a stratified medical treatment plan based on investigation findings (that is, spasm or coronary microvascular dysfunction) or standard care. Patients in the intervention arm showed improved angina status on the Seattle Angina Questionnaire summary score at six months (11.68 points, 95% confidence interval 4.99 to 18.37; $P=0.001$) and at one year (13.6 points; 7.3 to 19.9; $P<0.001$).^{13 14} The use of functional coronary angiography is further evident from other reports,^{15 16} where 80–90% of patients evaluated have had abnormal coronary haemodynamic findings, thereby providing explanations for their chest pain. Considering the clinical use of functional coronary angiography, its techniques have been recommended in professional society guidelines.¹⁷

Coronary macrovascular functional disorders (coronary artery spasm)

More than 60 years ago, Prinzmetal described 32 cases of “variant angina,” with features that differed

from the classic angina detailed by Heberden¹⁸ because the pain occurred at rest rather than being precipitated by exertion, and it was often associated with transient ST elevation rather than ST depression.¹⁹ Since this first description, improved understanding of the syndrome has evolved with the advent of coronary angiography confirming that epicardial coronary artery spasm was responsible for the syndrome. More recently, the disorder has been referred to as “vasospastic angina” with clinical diagnostic criteria including nitrate responsive angina, transient ischaemic ECG changes (either ST elevation or ST depression), and documented coronary artery spasm.²⁰ Although a spontaneous witnessed episode might confirm the diagnosis, provocative spasm testing during functional coronary angiography is often required. This testing involves incremental intracoronary doses of acetylcholine with coronary artery spasm confirmed on angiography. The importance of diagnosing vasospastic angina is its associated morbidity and mortality. Patients might experience recurrent disabling chest pain and could even develop acute myocardial infarction or sudden cardiac death.²¹ These adverse events could be prevented by effective treatment, so the diagnosis of vasospastic angina is imperative in the evaluation of patients with INOCA.

Coronary microvascular disorders

Coronary microvascular disorders are a frequent cause of INOCA but are less well understood and more complex than vasospastic angina; however, the two conditions might coexist, adding further complexity to the clinical picture. Vasospastic angina arises from exaggerated coronary artery constrictor response (attributable to vascular smooth muscle hyper-reactivity).^{22 23} By contrast, multiple mechanisms might be responsible for coronary microvascular disorders²⁴ such as an increased resting microvascular tone, microvascular spasm²⁵ (or hyper-reactivity), or a failure of the microvasculature to dilate in response to an increased myocardial oxygen demand.²⁶ These heterogeneous pathophysiological mechanisms have formed the basis of several coronary microvascular disorders, as summarised in table 1.

Cardiac syndrome X—this syndrome was one of the first coronary microvascular disorders described,²⁸ and initially specifically included patients with exertional chest pain, ischaemic ST depression on exercise stress testing, an absence of obstructive coronary artery disease, and no evidence of coronary artery spasm. It attracted considerable interest and important data over the past 30 years, but the term “cardiac syndrome X” has been progressively misused to describe any patient with INOCA. This confusion in the nomenclature and negative connotations for patients has prompted the avoidance of this diagnostic term; however, we have included it in this review because important clinical trials have been conducted in patients with specific criteria for the syndrome.

Microvascular angina—this term was initially used to describe patients who had chest pain

Table 1 | Clinical attributes of INOCA coronary vasomotor disorders

	Diagnostic investigation	Putative mechanism	Clinical presentation	Nitrate response
Coronary macrovascular disorders				
Vasospastic angina ²⁷	Spontaneous or inducible coronary artery spasm	Coronary artery spasm	Rest or unstable angina; smoking is a risk factor	Prompt
Coronary microvascular disorders ²⁴				
Cardiac syndrome X	Positive stress ECG	Impaired microvascular vasodilation	Stable exertional angina; high prevalence in female patients	Limited
Microvascular angina	Impaired coronary flow reserve	Impaired microvascular vasodilation	Often rest angina; often female patients	Limited
Coronary slow flow phenomenon	Delayed vessel opacification on angiography	Increased microvascular resistance	Unstable angina; smoking is a risk factor	Variable
Microvascular spasm	Inducible pain and ischaemic ECG changes with acetylcholine, but no coronary artery spasm	Microvascular spasm	Unstable angina; often female patients	Variable

ECG=electrocardiogram.

with an impaired coronary flow reserve (that is, less than a doubling of the coronary blood flow response to a standard hyperaemic stimulus) in the absence of obstructive coronary artery disease.²⁹ More recently, it has become the generic term for patients with a primary coronary microvascular disorder characterised by ischaemic chest pain, non-obstructive coronary arteries on angiography, evidence of myocardial ischaemia, and evidence of coronary microvascular dysfunction (eg, abnormal coronary flow reserve).³⁰

Coronary slow flow phenomenon—this event is an angiographic phenomenon characterised by the delayed passage of angiographic contrast in the absence of obstructive coronary arteries.³¹ This coronary microvascular disorder was the first to raise awareness that patients with coronary microvascular disorders might initially present with unstable angina, rather than a chronic stable angina presentation.³²

Microvascular spasm—this disorder is diagnosed when intracoronary acetylcholine during functional coronary angiography precipitates chest pain and ischaemic ECG changes but not epicardial coronary artery spasm, in patients without obstructive coronary artery disease.³³ Therefore, this coronary microvascular disorder is readily diagnosed during acetylcholine provocation testing, although its association with vasospastic angina is difficult to define.

What are the treatment targets?

Patients with INOCA have an increased risk of MACE and impaired health status, so treatment should be targeted at improving prognosis by preventing MACE, and improving quality of life by optimising symptom control (fig 1).

Prognostic target—reducing the risk of MACE

Among patients with INOCA, MACE has considerable heterogeneity, with a higher incidence in those individuals who have had typical angina or mild-to-moderate atherosclerotic disease on angiography.³ This heterogeneity in outcomes reflects the variation in the INOCA cohorts studied, since not all patients undergo comprehensive functional coronary angiography to delineate the multiple

pathophysiological mechanisms responsible for the vasomotor disorders.

Vasospastic angina

Vasospastic angina has long been associated with a risk of MACE, including acute myocardial infarction, malignant ventricular arrhythmias, and sudden cardiac death.²¹ Indeed, the Japanese Coronary Spasm Association has validated a risk score for predicting MACE in patients with vasospastic angina, with key clinical determinants including out-of-hospital cardiac arrest, obstructive coronary artery disease, rest angina, smoking, multivessel spasm, ST elevation during a spontaneous angina attack, and beta blocker use.⁶ Therefore, the prevention of MACE in vasospastic angina requires these risk factors to be managed (that is, cardiac arrest, coronary artery disease, smoking, and beta blocker use).

Coronary microvascular disorders

Coronary microvascular disorders provide a greater dilemma in targeting cardioprotective treatment to reduce MACE. Firstly, the increased risk of MACE in these disorders appears small, with some studies providing conflicting results. Secondly, the heterogeneous endotypes within this form of INOCA could differ in their risk of MACE and thus in their requirement for cardioprotective treatment. Finally, because functional coronary angiography is not done routinely, pathophysiological characteristics of the responsible underlying mechanism might be missed in many patients with INOCA. These compounding issues highlight the ongoing problems with identifying cardioprotective agents for these disorders.

Health status target—reducing angina symptoms to improve quality of life

In a novel investigation, the health status of patients with suspected INOCA were compared with those who had obstructive coronary artery disease associated with stable angina and with healthy controls.¹² The angina frequency, physical limitation, and quality of life in the 12 months after elective angiography for the investigation of chest pain was similar irrespective of the presence or absence of obstructive coronary artery disease (fig 4). Moreover, the only predictor of

ongoing chest pain at 12 months was female sex.¹² Furthermore, both physical and mental quality of life indices at 12 month follow-up were worse in patients with INOCA than in healthy controls with no history of chest pain.¹² Thus, improving health status is key in the treatment for INOCA, which should target improving angina symptoms since the frequency of angina is related to quality of life.³⁴

Targeting the control of angina symptoms can involve two approaches: an anti-ischaemic approach or an anti-nociceptive approach (table 2). Because the underlying mechanism responsible for the angina symptom is primarily believed to be ischaemic in nature, the anti-ischaemic approach to the underlying pathophysiology should be first considered; but in patients with chronic chest pain syndromes, the anti-nociceptive approach might also need to be used.

Anti-ischaemic approach

Pharmacological anti-ischaemic treatments

Pharmacological anti-ischaemic treatments can prevent or reduce ischaemia and thus improve symptoms. Conventional anti-ischaemic agents established in patients with stable angina and with obstructive coronary artery disease have also shown variable effectiveness in INOCA. These agents include long acting nitrates,^{35 36} beta blockers,³⁷ calcium channel blockers,^{37 38} ivabradine,³⁹ nicorandil,⁴⁰⁻⁴² ranolazine,^{38 39} perhexiline,⁴³ and trimetazidine⁴⁴ (tables 2, 3, and 4). They can achieve their anti-ischaemic effects by reducing myocardial oxygen demand (thereby reducing heart rate, blood pressure, cardiac contractility, or altering myocardial metabolism), or increasing coronary blood supply (by reducing contraction vascular smooth muscle cell and thus coronary tone). These anti-ischaemic agents

achieve their therapeutic effects via different targets (table 2) and hence are often used in combination. In addition to these conventional agents, novel anti-ischaemic agents have been shown to reduce ischaemia or angina in patients with INOCA including phosphodiesterase-3⁵⁷ and phosphodiesterase-5⁷⁶ inhibitors, rho kinase inhibitors,^{96 97} angiotensin converting enzyme inhibitors⁷² and estradiol,⁵⁴ as well as lifestyle risk factor modification^{87 91} (tables 3 and 4).

Non-pharmacological anti-ischaemic treatments

Non-pharmacological anti-ischaemic treatments of potential use are summarised in table 2. Exercise training has been shown to be beneficial in patients with INOCA, with the proposed mechanism being an improvement in endothelial function.⁹⁸ Stellate ganglion blockade or thoracic sympathectomy has been shown to reduce symptoms and ischaemic ECG changes in patients with vasospastic angina,⁹⁹ possibly by interrupting the influence of cardiac sympathetic efferent pathways on coronary vessels. However, whether this cardiac sympathectomy approach reduces symptoms by inhibiting coronary spasm or disrupting sympathetic pain afferents (that is, the nociceptive effect) remains unclear. Other anti-ischaemic devices that have been reported to improve symptoms in patients with coronary microvascular disorders include enhanced external counterpulsation¹⁰⁰ and the coronary sinus reducer¹⁰¹ (table 2).

Anti-nociceptive approach

Patients with coronary microvascular disorders have shown hyperalgesic responses to pain, irrespective of the presence of ischaemia.¹⁰² The hyperalgesic nociceptive pathway could arise from abnormalities at the level of pain receptors (adenosine might be a nociceptive stimulus), afferent sympathetic pain fibres, or unregulated pain transmission through the thalamus to the cortex.¹⁰² Accordingly, therapeutic strategies that modulate the pain pathway—by inhibiting nociceptive adenosine receptors with methylxanthines,¹⁰³ inhibiting afferent pain neurones with tricyclic antidepressants¹⁰⁴ or neurostimulators,¹⁰⁵ blocking pain transmission at the spinal cord level with analgesics or spinal cord stimulators,¹⁰⁶ or modulating cortical inputs with cognitive behaviour therapy¹⁰⁷—have been used in refractory angina. Therefore, this approach provides an alternative strategy to managing angina, particularly when it is refractory to anti-ischaemic treatments.

How to treat?

The above treatment targets for INOCA (that is, reducing the risk of MACE with cardioprotective agents and improving symptoms with anti-anginal treatments) need to be applied in the context of knowing who we are treating for INOCA (that is, those people with ischaemic chest pain due to coronary macrovascular spasm or microvascular dysfunction), so that the question of how to treat

Fig 4 | Health status over 12 months in patients investigated for chest pain with or without obstructive coronary artery disease. CAD=coronary artery disease; INOCA=ischaemia with non-obstructive coronary arteries. Adapted with permission from Tavella et al (2016)¹²

Table 2 | Potential anti-anginal treatments for ischaemia with non-obstructive coronary arteries

Anti-anginal treatment	Possible mechanisms and clinical effect
Anti-ischaemic targets	
Anti-ischaemic pharmacological treatments	
Beta blockers (eg, atenolol, metoprolol)	Inhibit myocardial beta 1 receptors (to reduce heart rate and contractility)
Calcium channel blockers, non-dihydropyridine (eg, verapamil, diltiazem)	Inhibit L calcium channels in myocardial cells to reduce heart rate and contractility in specialised conducting tissue to reduce heart and in VSMCs leading to vasodilation
Calcium channel blockers, dihydropyridine (eg nifedipine, amlodipine)	Inhibit L calcium channels in VSMCs (leading to vasodilation)
Long acting nitrates (eg, isosorbide dinitrate, isosorbide mononitrate)	Increase nitric oxide release (to increase cGMP levels in VSMCs, leading to vasodilation); more potent systemic venodilator (reducing preload) than arterial dilator; epicardial coronary vasodilator
Potassium channel activator (eg, nicorandil)	Open VSMC potassium ATP channels (leading to vasodilation); increase nitric oxide release (to increase cGMP levels in VSMCs, leading to vasodilation); balanced vasodilator in veins and arteries; epicardial and microvascular coronary vasodilator
Late sodium current blockers (eg, ranolazine)	Inhibit myocyte late sodium currents (to reduce sodium dependent calcium overload); believed to improve myocardial relaxation (thus reducing myocardial oxygen demand and improving microvascular perfusion)
Fatty acid oxidation inhibitors (eg, trimetazidine)	Shift cardiac metabolism from fatty acid oxidation to glucose oxidation (to reduce myocardial oxygen demand)
Sinus node inhibitors (eg, ivabradine)	Inhibit sinoatrial node I _c current (to reduce heart rate)
Angiotensin converting enzyme inhibitors (eg, enalapril)	Inhibit conversion of angiotensin I to II (leading to vasodilation)
Phosphodiesterase-3 inhibitors (eg, cilostazol)	Increase cAMP levels in VSMCs (leading to vasodilation)
Phosphodiesterase-5 inhibitors (eg, sildenafil)	Increase cGMP levels in VSMCs (leading to vasodilation); caution with nitrates owing to increased cGMP concentrations, which can lead to hypotension
Rho kinase inhibitors (eg, fasudil)	Inhibit VSMC rho kinase (to increase MLC dephosphorylation, leading to vasodilation)
Statins (eg, pravastatin, fluvastatin)	Increase endothelial nitric oxide release (to increase cGMP levels in VSMCs, leading to vasodilation); inhibit rho kinase pathway in VSMCs (to increase MLC dephosphorylation, leading to vasodilation)
Anti-ischaemic non-pharmacological treatments	
Stellate ganglion block	Reduces cardiac sympathetic tone (to reduce vasoconstriction); disrupts cardiac sympathetic pain afferent pathway
External counterpulsation	Promotes retrograde aortic diastolic coronary flow (to increase coronary perfusion); reduces left ventricular diastolic pressure (to reduce myocardial oxygen demand); increases blood flow (leading to endothelial homeostasis and increased endothelial function)
Coronary sinus reducer	Increases coronary venous pressure (leading to arteriolar dilation and increased perfusion)
Anti-nociceptive targets	
Tricyclic antidepressants (eg, imipramine)	Block noradrenaline reuptake (to inhibit pain modulating neurons, and reduce pain)
Methylxanthines (eg, theophylline)	Inhibit adenosine A _{2A} receptor (to reduce pain)
Opiates	Activate dorsal root ganglion and peripheral nerve opioid receptors (to reduce pain)
TENS unit	Transcutaneous electrical nerve stimulus (to block pain afferents (gate theory))
Spinal stimulator	Spinal cord stimulation (C ₇ /T ₁ , T ₁ /T ₂ ; to block pain afferents (gate theory))

VSMC=vascular smooth muscle cell; cGMP=cyclic guanosine monophosphate; cAMP=cyclic adenosine monophosphate; MLC=myosin light chain; TENS=transcutaneous electrical nerve stimulation.

is personalised for individual patients based on the underlying pathophysiological mechanisms responsible for INOCA (figs 1 and 5). Thus, specific pathophysiologically based treatment approaches are detailed below.

Establish the responsible pathophysiological mechanisms

Is it INOCA?

Before initiating treatment, doctors should be confident of the clinical diagnosis, so that non-cardiac and non-ischaemic causes of the chest pain can be excluded (figs 3 and 5). However, even in patients with an established coronary vasomotor disorder, discerning clinicians should continue to monitor for alternative causes, especially if chest pain characteristics have changed (eg, new gastro-oesophageal reflux). Moreover, patients can develop obstructive coronary artery disease over time, so this possibility should be reconsidered.

Is it macrovascular or microvascular dysfunction?

Although some INOCA treatments are effective in both coronary macrovascular and microvascular

dysfunction, others are more specific to one of these mechanisms. Hence treatments should be prescribed on the basis of clinical evidence, which targets one of these mechanisms or disease entities (table 3 and fig 5). As described above, functional coronary angiography would be a good diagnostic tool for evaluating the responsible pathophysiological mechanisms in patients with INOCA but is not often performed despite guideline recommendations.¹⁰⁸ Moreover, functional coronary angiography could reveal that a patient has both macrovascular and microvascular dysfunction.

In the absence of functional coronary angiography, classic clinical presentations might assist doctors in distinguishing vasospastic angina from coronary microvascular disorders; however, these traditional methods have not undergone rigorous validation. The classic features of vasospastic angina are rest angina with ST elevation, both rapidly resolving with sublingual nitrates. Nocturnal angina and an association with migraines have also been reported.¹⁰⁹ In contrast, syndrome X is classically described as pain occurring on effort, which has a variable response to sublingual nitrates and frequently occurs

Table 3 | Vasospastic angina studies

Study	No	Intervention	Inclusion criteria	Coronary microvascular dysfunction	Study design	Impact on outcomes
Calcium channel blockers						
Heupler (1979) ⁴⁵	8	Nifedipine	Rest angina, NOCA, transient STE	Bedside test	Observational, non-randomised	Nifedipine reduced mean monthly angina episodes from 104 to eight
Ascherman (1990) ⁴⁶	17	Nifedipine	Angina, NOCA, transient STE	Spontaneous spasm on angiography	Double blind, comparative crossover RCT	Nifedipine reduced mean weekly angina episodes from 43 to eight, after six weeks ($P<0.001$)
Chahine (1993) ⁴⁷	52	Amlodipine	Rest angina, transient STE	Provoked spasm on angiography or beside	Double blind, placebo controlled, crossover RCT	Amlodipine reduced mean daily angina episodes by 55% (placebo=15%) at four weeks ($P=0.009$)
Higuma (2010) ⁴⁸	37	Nifedipine CR; diltiazem R	Rest angina, NOCA, ischaemic ECG	Provoked spasm on angiography	Open label, comparative RCT	Mean weekly angina episodes reduced over 12 weeks for nifedipine (2.6 to 0.4, $P<0.05$) and diltiazem (2.7 to 0.3, $P<0.05$)
Oikawa (2010) ⁴⁹	30	Nifedipine; benidipine	Rest angina, NOCA, ischaemic ECG	Provoked spasm on angiography	Comparative RCT	Nifedipine reduced mean weekly angina episodes from 3.5 ($SD\pm 7.7$) to 0.1 (± 0.4), at 8 weeks ($P<0.001$); benidipine did not improve angina episodes (1.4 (± 1.1) to 0.6 (± 0.8), $P>0.5$)
Kook (2020) ⁵⁰	48	Diltiazem; nebivolol	Rest angina, NOCA	Provoked spasm on angiography	Double blind, parallel group RCT	Change (%) in diameter from baseline acetylcholine provocation test. Suppression of acetylcholine constriction: diltiazem ($68\pm 13\%$), nebivolol ($50\pm 8\%$), diltiazem + nebivolol ($47\pm 12\%$) at 12 weeks ($P=0.054$); SAQ scores improved in overall study population (80.3 ± 7.9 to 85.4 ± 7.8 , $P<0.001$); no significant difference in SAQ between diltiazem and nebivolol
β adrenergic agents						
Shimizu (1993) ⁵¹	10	Denopamine	Rest angina, NOCA, ischaemic ECG	Provoked spasm on angiography	Placebo controlled RCT	Denopamine reduced mean daily angina frequency compared with placebo (0.6 ($SD\pm 1.2$) v 2.2 (± 1.3), $P<0.005$)
Long acting nitrates						
Ascherman (1990) ⁴⁶	17	Isosorbide dinitrate	Angina, NOCA, transient STE	Spontaneous spasm on angiography	Double blind, comparative, crossover RCT	Isosorbide dinitrate reduced mean weekly angina episodes from 43 to four, after six weeks ($P<0.001$)
Potassium channel openers						
Kishida (1987) ⁴¹	32	Nicorandil	Angina, NOCA, transient STE	NA	Single blind, placebo controlled, crossover RCT	Nicorandil reduced mean daily angina episodes compared to placebo (placebo=mean 3.6 ($SE\pm 0.4$) per day, nicorandil= 0.7 (± 0.2) per day, $P<0.001$)
Lablanche (1992) ⁴²	13	Nicorandil; nifedipine	Angina, NOCA, transient STE	Spontaneous or provoked spasm on angiography	Single blind, placebo controlled, crossover RCT	Nicorandil suppressed inducible spasm in 92% of patients (all inducible on placebo); nifedipine suppressed inducible spasm in 69% of patients (all inducible on placebo)
Statins						
Yasue (2008) ⁵²	64	Fluvastatin	Angina, NOCA, positive stress test, background CCB treatment	Acetylcholine induced spasm on angiography	Open label RCT	75% of patients in the fluvastatin group became asymptomatic after 6 months ($P<0.001$), compared to 70% of control patients ($p<0.001$)
Kim (2019) ⁵³	100	Atorvastatin; sarpogrelate	Chest pain, NOCA, substantial ST-T wave change	Provoked spasm on angiography	Placebo controlled RCT with 2x2 design	Atorvastatin and sarpogrelate did not affect readmission rate compared with placebo (sarpogrelate + atorvastatin 47%, sarpogrelate 58%, atorvastatin 40% and placebo 56%, $P=0.74$)
Oestrogens						
Kawano (2001) ⁵⁴	15	17- β oestradiol	Rest angina, NCA, transient ST elevation	Provoked spasm on angiography	Placebo controlled RCT	17- β oestradiol suppressed hyperventilation induced angina in all patients on the third day of supplementation
Exercise therapy or lifestyle						
Morikawa (2013) ⁵⁵	26	Exercise training	Rest angina, NOCA, ischaemic ECG	Provoked spasm on angiography	Non-randomised intervention	Exercise training improved median angina episodes from 2 (IQR 1-7) to 0 (0-2) at five days ($P<0.001$)
Novel agents						
Huckell (1981) ⁴³	18	Perhexiline	Rest angina, STE	Transient ST elevation, spasm on angiography in 13	Non-randomised interventions	Perhexiline reduced angina episodes
Morita (2014) ⁵⁶	73	Pioglitazone	Rest angina, NOCA, ischaemic ECG, background CCB treatment	Acetylcholine induced spasm on angiography	Open label RCT	Pioglitazone improved angina episodes by 75% but was not different compared to placebo (74%, $P<0.001$) at six months
Shin (2014) ⁵⁷	50	Cilostazol	Chest pain, NOCA, ischaemic ECG, background CCB treatment	Provoked spasm on angiography	Double blind, placebo controlled, RCT	Cilostazol reduced weekly angina episodes (mean 66 $SD\pm 87\%$) compared to placebo ($18\pm 140\%$, $P=0.009$) at six months

NOCA=non-obstructive coronary arteries; NCA=normal coronary arteries; STE=ST segment elevation; RCT=randomised clinical trial; CFR=coronary flow reserve; CSFP=coronary slow flow phenomenon; SAQ=Seattle Angina Questionnaire; CR=cardiac rehabilitation; R=sustained release; ECG=electrocardiogram; CCB=calcium channel blockers; NA=not available; SD=standard deviation; SE=standard error; IQR=interquartile range.

Table 4 | Coronary microvascular disorder studies

	No	Intervention	Inclusion criteria	Coronary microvascular dysfunction	Study design	Impact on outcomes
Calcium channel blockers						
Cannon (1985) ⁵⁸	26	Verapamil; nifedipine	Chest pain, NCA	Abnormal CFR	Double blind, placebo controlled, crossover RCT	CCBs improved angina episodes compared to placebo (mean 21 SD±21 v 35±27, P<0.001)
Cannon (1990) ⁵⁹	11	Lidoflazine	Chest pain, NCA	Abnormal CFR	Double blind, placebo controlled, RCT	Lidoflazine did not affect angina episodes (mean -9 SD±37, P>0.05) at seven weeks
Beltrame (2004) ⁶⁰	20	Mibefradil	Angina, NOCA	CSFP	Double blind, placebo controlled, crossover RCT	Mibefradil reduced monthly angina episodes by 56% compared to placebo (P<0.001)
Zhang (2014) ⁶¹	66	Diltiazem; fluvastatin	Angina, NCA, positive stress test	Not required	Randomised trial	Diltiazem + fluvastatin improved mean exercise time at 90 days compared to either drug alone (mean 446 SD±164 v 250±104 seconds, P<0.05)
Beta adrenergic agents						
Lanza (1999) ³⁵	10	Atenolol; amlodipine; isosorbide mononitrate	Exercise angina, NCA, positive stress test	Not assessed	Double blind, placebo controlled, comparative RCT	Atenolol reduced monthly angina episodes from mean 24 (SD±18) to 15 (±13); P<0.05; amlodipine and isosorbide mononitrate had no impact on angina episodes
Sen (2009) ⁶²	38	Nebivolol; metoprolol	Angina, NCA, transient ST depression during exercise	Not required	Single blind RCT	Nebivolol improved CCS angina class in 73% patients and total exercise time; metoprolol improved CCS angina class in 47% patients but did not affect exercise
Long acting nitrates						
Bugiardini (1993) ⁶³	16	Isosorbide dinitrate	Angina, NCA, positive stress test	Not required	Non-randomised intervention	Isosorbide dinitrate decreased time to angina on exercise testing compared to baseline (mean 477 SD±93 v 561±108 seconds, P<0.002)
Russo (2013) ⁶⁴	29	Isosorbide dinitrate	Angina, NCA, positive stress test	Not required	Non-randomised intervention	Isosorbide dinitrate did not affect exercise duration
Potassium channel openers						
Yamabe (1995) ⁶⁵	11	Nicorandil	Angina, NCA, positive stress test	Not required	Non-randomised intervention	Nicorandil improved the extent of ischaemia score on ²⁰¹ Thallium scintigraphy (before, mean 0.37 SD±0.22; after, 0.20±0.15; P<0.05)
Chen (1997) ⁴⁰	13	Nicorandil	Angina, NCA, positive stress test	Abnormal CFR	Double blind, placebo controlled, crossover RCT	Nicorandil improved total exercise time (mean 443 SD±78 v 405 ±64 seconds, P=0.036) and time to 1 mm ST depression (342±104 v 273±72 seconds, P=0.026) compared with placebo
Statins						
Kayikcioglu (2003) ⁶⁶	40	Pravastatin	Angina, NCA, positive stress test	Not required	Single blind, placebo controlled RCT	Pravastatin improved mean exercise time (mean 530 SD±162 v 585±165 seconds, P<0.05) and time to 1 mm ST depression (267±105 v 419±162 seconds, P<0.05) at 90 days
Fabian (2004) ⁶⁷	40	Simvastatin	Angina, NCA, positive stress test	Not required	Open label, placebo controlled RCT	Simvastatin improved time to 1 mm ST depression (mean 4.45 SD±0.39 v 5.33±0.27 minutes, P<0.001) at 12 weeks, but was unchanged with placebo
Oestrogen						
Bairey Merz (2010) ⁶⁸	35 WO	Norethindrone or ethinyl estradiol	Angina, NOCA, positive stress test	Abnormal CFR	Double blind, placebo controlled RCT	Oestrogen treatment increased angina-free status compared to placebo (41% v 22% angina free, P=0.02) at 12 weeks
Renin/angiotensin/aldosterone inhibitors						
Kaski (1994) ⁶⁹	19	Enalapril	Angina, NCA, positive stress test	Abnormal CFR	Single blind, placebo controlled, crossover RCT	Enalapril improved total exercise time (mean 779 SD±141 v 690 ±148 seconds, P=0.006) at two weeks
Motz (1996) ⁷⁰	15	Enalapril	NCA, abnormal resting ECG or positive stress test	Not required	Non-randomised intervention	Enalapril improved CCS angina class (mean 2.5 SD±0.6 to 1.5 ±0.6, P<0.01) at 12 months
Chen (2002) ⁷¹	20	Enalapril	Angina, NCA, positive stress test	Not required	Double blind, placebo controlled RCT	Enalapril reduced weekly angina episodes (mean 1.6 SD±0.5 v 0.5 ±0.4, P<0.05) at eight weeks
Pauly (2011) ⁷²	78	Quinapril	Angina, NOCA	Abnormal CFR	Double blind, placebo controlled RCT	Quinapril reduced angina episodes at 16 weeks compared to placebo (P=0.037)
Bavry (2014) ⁷³	41 WO	Eplerenone	Angina, NCA, positive stress test	Abnormal CFR	Double blind, placebo controlled RCT	Eplerenone did not affect angina episodes at 16 weeks, compared with placebo
Michelsen (2018) ⁷⁴	63 WO	Ramipril	Angina, NCA, not required	Abnormal CFR	Double blind, placebo controlled RCT	Ramipril did not affect angina episodes at 24 weeks, compared with placebo
Nitric oxide modulators						
Lerman (1998) ⁷⁵	26	L-arginine infusion	Chest pain, NOCA	Not assessed	Double blind, placebo controlled RCT	L-arginine improved qualitative symptom scores compared with placebo (P<0.05)
Denardo (2011) ⁷⁶	23	Sildenafil	Chest pain, NOCA	CFR ≤3.0	Non-randomised intervention	Sildenafil improved CFR in patients with baseline CFR <2.5

(Continued)

Table 4 | Continued

	No	Intervention	Inclusion criteria	Coronary microvascular dysfunction	Study design	Impact on outcomes
α adrenergic agents						
Cannon (1994) ⁷⁷	60	Clonidine; imipramine	Refractory chest pain, NCA	Not required	Double blind, placebo controlled RCT	Imipramine reduced mean angina episodes by mean 52 (SD±25%) at three weeks (P=0.03); clonidine had no impact on angina episodes
Bøtker (1998) ⁷⁸	16	Doxazosin	Angina, NCA, positive stress test	Not assessed	Double blind, placebo controlled, crossover RCT	Doxazosin did not affect exercise induced angina at 10 weeks
Rosen (1999) ⁷⁹	15	Doxazosin	Angina, NCA, positive stress test	Not required	Double blind, placebo controlled RCT	Doxazosin did not affect total exercise time or time to 1 mm ST depression compared to placebo, at seven days
Novel anti-anginal agents						
Total (2006) ⁸⁰	48	Trimetazidine	Ischaemic symptoms, NCA	CSFP	Double blind, placebo controlled RCT	Trimetazidine improved exercise time to angina (before, mean 339 SD±73 v after, 421±71 seconds; P=0.02) and the number of angina-free patients at four weeks, compared to placebo (P=0.03)
Mehta (2011) ³⁸	20 WO	Ranolazine	Angina, NOCA, positive stress test	Abnormal CFR	Double blind, placebo controlled, crossover RCT	Ranolazine improved angina related physical limitation compared to placebo (SAQ physical limitation scores, median 92 (range 79-98) v 83 (67-97); P=0.046) but not angina frequency
Villano (2013) ³⁹	45	Ranolazine; ivabradine	Exercise angina, NOCA, positive stress test	Abnormal CFR	Double blind, placebo controlled RCT	Ranolazine improved SAQ angina frequency at four weeks (mean 61 SD±12 v 81±17) to a greater extent than ivabradine (64±14 v 73±18) or placebo (73±17 v 71±18; P<0.001)
Bairey Merz (2016) ⁸¹	128 WO	Ranolazine	Suspected ischaemia, NOCA, positive stress test	Abnormal CFR	Double blind, placebo controlled, crossover RCT	Ranolazine SAQ angina frequency at two weeks was not different to placebo (mean difference -0.08 (95% confidence interval -4.18, 4.34), P=0.97)
Ahmed (2017) ⁸²	7	Ranolazine	Angina, NOCA, positive stress test	Abnormal index of microvascular resistance	Non-randomised intervention	Ranolazine improved SAQ angina frequency scores at four weeks compared to baseline (P=0.04)
Rambarat (2019) ⁸³	81	Ranolazine	Angina, NOCA, positive stress test	Abnormal CFR	Double blind, placebo controlled, crossover RCT	Ranolazine improved SAQ angina frequency compared to placebo (mean difference 5.76 SD±11.51 v -0.86±13.54, confidence interval 0.28 to 12.96, P=0.007) at two weeks, in patients with low CFR
Lim (2017) ⁸⁴	19	Allopurinol	Angina, NCA, positive stress test	Not required	Double blind, placebo controlled, crossover RCT	Allopurinol did not affect total exercise time, compared with placebo
Exercise therapy or lifestyle factors						
Eriksson (2000) ⁸⁵	26	Exercise training	Angina, NCA, positive stress test	Not required	Parallel design (usual care) RCT	Exercise training improved time to angina relative to baseline (mean 4 SD±1 v 6±1 minute, P=0.01)
Tyni-Lenne (2002) ⁸⁶	24 WO	Exercise training	Angina, NCA, positive stress test	Not required	Parallel design (usual care) RCT	Exercise training improved walk distance relative to baseline (mean 555 SD±47 v 587±49 metres, P<0.006)
Asbury (2008) ⁸⁷	64 WO	Cardiac rehabilitation	Chest pain, NCA, positive stress test	Not required	Parallel design (usual care) RCT	Cardiac rehabilitation improved symptom severity at eight weeks (before, mean 2.0 SD±0.8 v after 1.26±1.1, P=0.009)
Fiezi (2012) ⁸⁸	40	Cardiac rehabilitation	Angina, NCA, positive stress test	Not required	Parallel design (usual care) RCT	Cardiac rehabilitation improved physical functioning scores compared to controls (mean 59 SD±8 v 36±13, P<0.05)
Fiezi (2012) ⁸⁸	40	Relaxation therapy	Angina, NCA, positive stress test	Not required	Parallel design (usual care) RCT	Relaxation therapy improved physical functioning scores compared to controls (mean 51 SD±13 v 30±9, P<0.05)
de Carvalho (2015) ⁸⁹	12	Exercise training	Angina, NCA, positive stress test	Not required	Non-randomised intervention	Exercise training improved physical functioning scores relative to baseline (mean 88 SD±9 v 45±26, P<0.001).
Szot (2015) ⁹⁰	55 WO	Cardiac rehabilitation	Angina, NOCA, positive stress test	Not required	Non-randomised intervention	Cardiac rehabilitation improved exercise duration of exercise relative to baseline (mean 760 SD±142 v 636±157 seconds, P<0.001)
Bove (2020) ⁹¹	56 WO	Exercise and risk factor control	Angina, NOCA	Abnormal CFR	Parallel design (usual care) RCT	Lifestyle risk factor control improved SAQ angina frequency scores compared to usual care (difference 12.91 (95% CI 4.91 to 20.90), P=0.002)
Devices						
Eliasson (1993) ⁹²	12	Spinal cord stimulation	Angina, NCA, positive stress test	Not assessed	Non-randomised intervention	Spinal cord stimulation improves exercise test time to angina (before 2.7 ±1.9, after 5.4 ±2.2 minutes, P<0.01) and time to 1 mm ST depression (before 2.4 ±1.6, after 3.5 ±1.9 minutes, P<0.01)
Jessurun (2003) ⁹³	8	TENS	Angina, NCA, positive stress test	Not assessed	Non-randomised intervention	TENS reduced angina episodes at four weeks relative to baseline (mean 20 SE±3 v 3±1, P=0.01)
De Vries (2007) ⁹⁴	24	TENS/spinal cord stimulation	Refractory angina, NOCA	Not assessed	Non-randomised intervention	TENS, followed by spinal cord stimulator, if TENS caused skin irritation, improved SAQ angina frequency (mean 42 SD±24 to 55±23; P=0.005)
Luo (2012) ⁹⁵	45	EECP	Angina, NCA	Abnormal CFR	Non-randomised intervention	EECP improved CCS angina class at eight weeks, relative to baseline (mean 2.96 SD±0.69 to 1.75 ±0.85, P<0.001).

NOCA=non-obstructive coronary arteries; NCA=normal coronary arteries; STE=ST segment elevation; RCT=randomised clinical trial; CFR=coronary flow reserve; CSFP=coronary slow flow phenomenon; SAQ=Seattle Angina Questionnaire; WO=women only; CCB=calcium channel blockers; CCS=Canadian Cardiovascular Society; TENS=transcutaneous electrical nerve stimulation; EECP=enhanced external counterpulsation; ECG=electrocardiogram; SD=standard deviation; SE=standard error.

Fig 5 | How to treat patients with INOCA—a personalised medicine approach. CT=computed tomography

in women. Patients with microvascular angina can experience rest angina, atypical symptoms, or episodes triggered by emotional stress.¹¹⁰ While the classic clinical presentations might be useful in delineating the pathophysiological syndromes, functional coronary angiography is a more objective modality.

Avoid precipitating and aggravating factors

Smoking

Except for smoking, the conventional cardiovascular risk factors are less prevalent in patients with INOCA

than in those with obstructive coronary artery disease. However, smoking is a key risk factor for vasospastic angina,¹⁰⁹ where its cessation is strongly recommended.

Sympathomimetic agents

These agents include the recreational use of cocaine,¹¹¹ methamphetamines (ice),¹¹² and methylenedioxy-N-methamphetamine (ecstasy),¹¹³ all of which could precipitate vasospastic angina episodes. In addition, therapeutically used sympathomimetic agents (adrenaline,¹¹⁴

noradrenaline, and methylphenidate¹¹⁵) have been associated with precipitating episodes of coronary spasm.

Beta blockers

These agents have been reported to precipitate episodes of vasospastic angina by augmenting unopposed catecholamine alpha constrictor effects, and thus should be avoided in these patients.¹¹⁶ In contrast, beta blockers have been reported to improve angina in patients with coronary microvascular dysfunction³⁵; reflecting the importance in delineating the different pathophysiological mechanisms.

Other drug treatments

Ergot alkaloids¹¹⁷ and serotonin¹¹⁸ have been used as provocative stimuli in spasm testing. Hence ergot preparations used in the treatment of migraine¹¹⁹ or uterine bleeding¹²⁰ and serotonin uptake inhibitors used in treating depression¹²¹ could precipitate coronary spasm. Some chemotherapy agents (5-fluorouracil,¹²² capecitabine,¹²³ sorafenib¹²⁴) have also been described to precipitate episodes of vasospastic angina. General anaesthesia has been associated with inducing coronary spasm,¹²⁵ although the multiple agents used make it difficult to discern which particular agents are involved. Accordingly, the above drug treatments should be avoided or used with caution in patients with vasospastic angina. Their impact on coronary microvascular disorders is less clear.

Mental stress

Pathophysiological studies have shown that mental stress could provoke epicardial coronary artery constriction,¹²⁶ coronary microvascular dysfunction,¹²⁷ myocardial ischaemia,^{128–129} and angina¹²⁷ in the absence of obstructive coronary artery disease. These findings might explain why many patients with INOCA report that mental stress precipitates or aggravates their symptoms. In addition, clinical studies have reported an association between INOCA and anxiety disorders,^{130–133} as well as depression.^{131–132} What is unknown is whether these psychiatric disorders predispose to INOCA or the suboptimal management of INOCA precipitates these disorders. Regardless, mental stress should be avoided or minimised in patients with INOCA.

Cardioprotective treatments

Vasospastic angina

Calcium channel blockers are considered a key treatment for vasospastic angina because they have been shown to be an independent determinant of infarct-free survival,³⁷ and their cessation is associated with an increased risk of MACE.²¹ As for other anti-vasospastic agents (such as nitrates or nicorandil), evidence to support their routine use as cardioprotective agents is insufficient, in addition to concerns that chronic nitrate use might increase MACE owing to nitrate tolerance.¹³⁴ Furthermore,

implantable cardioverter defibrillators as a sudden death preventive measure might be warranted for patients with vasospastic angina who present with cardiac arrest or malignant arrhythmias. No randomised trials have examined the impact of implantable cardioverter defibrillators in this scenario, and small observational studies have yielded conflicting data.^{135–137}

Coronary microvascular disorders

Advice for coronary microvascular disorders is more challenging because no clinical trial data exist to support the use of cardioprotective agents, although statins and angiotensin converting enzyme inhibitors are often recommended in clinical guidelines,¹⁰⁸ and these treatments are the focus of a large prospective clinical trial that is in progress.¹³⁸

Anti-anginal treatments

Vasospastic angina

In addition to cardioprotective benefits, calcium channel blockers are effective at reducing angina symptoms in these patients.²¹ Long acting nitrates have also been traditionally used in the anti-anginal management of vasospastic angina, especially given that the pain is responsive to nitrates²¹; however, as stated above, their benefits have recently been questioned.¹³⁴ Other novel agents with clinical randomised controlled trial data supporting their use as anti-anginal agents in vasospastic angina include nicorandil^{41–42} and cilostazol⁵⁷ (table 3). In addition, aerobic exercise training has been shown to reduce angina episodes in patients with vasospastic angina.⁵⁵

Coronary microvascular disorders

The use of anti-anginal treatments in coronary microvascular disorders is more complex considering the multiple pathophysiological mechanisms, clinical subtypes, and heterogeneity in trial results. Nitrates, for example, could further impair coronary blood flow⁶³ and aggravate symptoms in patients with these disorders. Consequently, unlike vasospastic angina, no uniform first line treatment exists. Table 4 summarises the anti-anginal clinical trial evidence base currently available. The choice of agent will need to be based on clinical assessment as to:

- The suspected underlying mechanism—ischæmia (due to impaired vasodilation, resting constriction, or hyper-reactivity) versus hyperalgesia/nociception (attributable to a defective pathway at the level of the receptor, afferent nerves, spinal cord, or higher centres)
- The angina pattern—exertional angina (where heart rate reduction might be beneficial), rest angina (where coronary microvascular vasodilators might be more beneficial), or mixed pattern angina (that is, exertional and rest angina episodes)
- The concurrent disorders (eg, asthma, where β blockers are contraindicated).

In contrast to pharmacological anti-anginal treatments, exercise training, cardiac rehabilitation, and relaxation therapy have consistently shown benefit in coronary microvascular disorders (table 4). Such benefits include improved angina control^{85–87} and increased exercise capacity.^{88–90}

When to treat?

With knowledge of the INOCA treatment targets, the heterogeneous patient population, and how to tailor treatments to individual patients (personalised medicine), it is important to consider when is best to initiate the various treatments (fig 1). This approach will also need to be personalised, depending on the patient's progress.

Initial diagnosis

The diagnosis of INOCA requires the documentation of non-obstructive coronary arteries; therefore, it is most frequently diagnosed immediately after coronary angiography. In patients with vasospastic angina, calcium channel blockers should be immediately commenced, owing to their cardioprotective effects, although no definitive evidence exists for the benefits of cardioprotective agents in coronary microvascular disorders. Initiating anti-anginal treatment in patients with INOCA after diagnostic angiography will depend on the patients' symptomatic status, which will vary according to the treating clinician's threshold for performing angiography. For individuals with infrequent mild symptoms, the clinician and patient could decide to observe the patient's progress, using only short acting nitrates during acute episodes, before initiating regular maintenance anti-anginal treatments. However, for patients with more disabling pain, anti-anginal treatments should be promptly initiated, targeting the underlying pathophysiological mechanisms. As a guide to when to commence anti-anginal treatments, the angina frequency can provide a useful clinical surrogate.

As shown in fig 6, a linear relation exists between angina frequency and other markers of health status (physical limitation and quality of life), with a substantial step between monthly and weekly angina episodes. Hence a potential clinical threshold for considering when to initiate anti-anginal treatments is when angina episodes occur at least once a week. However, patients will differ in their perception of the angina symptoms, so treatment decisions should be personalised and considered via a shared decision making process.

Clinical monitoring of health status

Patients with vasospastic angina have long been recognised to have so-called hot phases, when the angina episodes are recalcitrant and difficult to manage, as well as so-called cold phases, when the disorder is quiescent.¹⁰⁹ This fluctuating pattern is likely to represent periodic changes in the underlying pathophysiology and precipitants. Although not as clearly documented, this pattern might also occur

in coronary microvascular disorders. Because the anti-anginal treatments are targeted towards INOCA symptoms, there could be quiescent periods when these treatments can be cautiously scaled back.

When following up patients, clinicians should be aware that they often overestimate the efficacy of their treatments. In chronic stable angina studies, clinicians frequently perceived the patient's angina as being optimally controlled, whereas the patient's perception was not as positive.³⁴ This discordance in perception is attributable to clinicians underestimating the angina burden, because 42% of patients report more angina than noted by their clinicians.¹³⁹ Variation in clinician skills for obtaining an angina history might account for these differences and could be minimised by a standardised angina collection tool to optimise clinical care.¹³⁹

Managing refractory angina

Patients with INOCA who have refractory angina (that is, who are unresponsive to two or more anti-anginal treatments) are likely to need particularly challenging clinical management. Firstly, doctors should consider whether the patient has developed obstructive coronary artery disease, which opens up more therapeutic options (that is, revascularisation treatments). Secondly, functional coronary angiography should be considered if not already performed, because the confirmation of vasospastic angina would guide clinicians to the more aggressive use of specific anti-anginal treatments. For example, case reports of high dose calcium channel blockers in patients with vasospastic angina have reported considerable benefits.^{140–141} Thirdly, patients who have a suboptimal response to conventional pharmacological anti-ischaemic agents warrant consideration for anti-nociceptive and non-pharmacological treatments (tables 2 and 3). Initiating these treatments will be based on the patient's health status and should be undertaken in a shared decision making model of care, especially considering the limited evidence base

Fig 6 | Associations between angina frequency, physical limitations, and quality of life. Data taken from Beltrame et al³⁴

available. Moreover, a care plan is often useful in patients who frequently present to hospital with uncontrolled angina to facilitate prompt initiation of appropriate treatment and avoid misplaced management approaches by hospital staff unfamiliar with the patient. In addition, involvement of a pain management unit will be beneficial for patients with chronic symptoms. These multidisciplinary teams have extensive experience in managing refractory pain syndromes and have access to valuable resources such as specialised clinical psychologists or psychiatrists, as well as multiple anti-nociceptive treatments (table 2).

Where to next—emerging treatments

Although calcium channel blockers have been well established as the first line agent in vasospastic angina, the optimal first-line treatment for coronary microvascular disorders remains elusive. Contemporary clinical trial approaches have used pharmacological treatments and novel treatment strategies.

These emerging treatments will provide a broader array of tools in managing angina secondary to epicardial coronary spasm or coronary microvascular dysfunction. Although study results of these important innovations are yet to come, the progress of many studies has been delayed by the covid-19 pandemic.

Intense medical treatment

Intense medical treatment (that is, high intensity statins plus angiotensin converting enzyme inhibitors or angiotensin receptor blockers) could reduce MACE in patients with INOCA. The WARRIOR trial is a multicentre study with a PROBE design (prospective, randomised, open-label with blinded-endpoint analysis) comparing intensive medical treatment with usual care in patients with INOCA, evaluating MACE (death, non-fatal myocardial infarction or stroke, or hospital admission for angina or heart failure) at an average follow-up period of three years.¹³⁸ Study completion is anticipated within the next few years when it will provide important insights into the potential benefits of conventional cardioprotective treatments in INOCA.

Ticagrelor

The TIC (ticagrelor in coronary microvascular dysfunction) trial (Australian and New Zealand Clinical Trials ACTRN12616000388415) evaluates the potential anti-anginal benefits of this anti-platelet agent in the coronary slow flow phenomenon. Ticagrelor inhibits erythrocyte adenosine uptake, thereby increasing plasma adenosine levels, which inhibits purinergic 2 (P_2) platelet receptors to exert an anti-platelet effect. The raised endogenous adenosine levels also stimulate the purinergic 1 (P_1) receptors, which includes the A_{2A} receptor, resulting in coronary microvascular vasodilation. The TIC trial uses a randomised, double blind, placebo controlled crossover design to examine the anti-anginal effects

of ticagrelor (90 mg twice daily) in patients with symptoms with the coronary slow flow phenomenon. The study findings should be available in two years and potentially provide another anti-anginal strategy for coronary microvascular disorders.

Endothelin receptor blockers

Endothelin receptor blockers could be of benefit in coronary microvascular disorders because endothelin is a potent coronary microvascular constrictor. Zibotentan is a specific endothelin A receptor antagonist and is being examined in two contemporary randomised clinical trials. The first trial (ACTRN12618000021279) uses the same design as the TIC trial (see above) to evaluate the anti-anginal effects of zibotentan (10 mg daily) in patients with symptoms with the coronary slow flow phenomenon. The second trial (the PRIZE (precision medicine with zibotentan in microvascular angina) trial; ClinicalTrials.gov NCT04097314) uses a randomised, double blind, placebo controlled crossover design to examine the impact of zibotentan (10 mg daily) on treadmill exercise time in patients with microvascular angina. Results from both trials should be available within two years.

Rhodiola rosea

Rhodiola rosea is a traditional herbal medicine that has multiple pharmacological properties attributed to its major active ingredient, salidroside. These properties include anti-oxidant and anti-inflammatory effects, but of particular relevance to patients with INOCA is its ability to block calcium channels in vascular smooth muscle cells.¹⁴² Accordingly, a randomised, double blind, placebo controlled trial is in progress to assess the impact of *Rhodiola rosea* capsules on coronary flow reserve and symptoms, in patients with INOCA symptoms with an impaired coronary flow reserve (NCT04218916). The efficacy of this herbal medicine should be evident in the next two years.

Autologous CD34 stem cells

Autologous CD34 stem cells administration has been shown to improve treadmill exercise time and angina frequency in randomised, double blind, placebo controlled trials among patients with obstructive coronary artery disease.¹⁴³ This benefit is attributable to the stem cells differentiating into endothelial cells and potentially releasing angiogenic cytokines that aid microvascular recovery. Moreover, a preliminary feasibility study in patients with INOCA suggests that they might also benefit from this treatment.¹⁴⁴ Based on these findings, the FREEDOM study has been initiated (NCT04614467); a randomised double blind, placebo controlled study evaluating the effect of one intracoronary administration of autologous CD34 stem cells on coronary flow reserve and angina frequency. The results of this novel strategy should be available in the next two years and will affect future therapeutic approaches in patients with INOCA.

Coronary sinus reducer

The coronary sinus reducer (Reducer, Neovasc) is balloon expandable, stainless steel, hourglass shaped endoluminal device, which is percutaneously implanted into the coronary sinus to increase coronary venous pressure thereby reducing coronary microvascular resistance. A previous clinical trial in patients with refractory angina and obstructive coronary artery disease has confirmed its benefit in alleviating refractory angina symptoms,¹⁴⁵ as has a recent preliminary study in patients with INOCA.¹⁴⁶ Within two to three years, the open label COSIMA trial (NCT04606459) will be completed, which compares the impact of device implantation and medical treatment on angina status in patients with INOCA. If effective, this single procedure, percutaneous intervention could provide another tool for the management of angina in patients with INOCA.

Guidelines

No professional society guidelines exclusively focus on INOCA, but the European Association of Percutaneous Cardiovascular Interventions, in collaboration with European Society of Cardiology (ESC) and COVADIS, have recently published a contemporary consensus document on INOCA.¹⁴⁷ This consensus document complements the present review by elaborating on diagnostic approaches in INOCA.

The 2019 ESC guidelines on the diagnosis and management of chronic coronary syndromes¹⁷ have a section regarding INOCA. Specific guideline recommendations have been published in relation to the investigation of vasospastic angina and microvascular angina. For patients with suspected vasospastic angina, class I recommendations include an ECG during anginal episodes and coronary artery imaging (invasive angiography or coronary CT angiography) to determine the extent of underlying atherosclerotic disease. Class IIa recommendations for these patients include ambulatory ST-segment monitoring and intracoronary provocative spasm testing.¹⁷ For patients with suspected microvascular angina, a class IIa recommendation includes guidewire based, invasive coronary flow reserve or microvascular resistance measures in patients with non-obstructive coronary arteries. Class IIb recommendations include intracoronary acetylcholine assessment for microvascular spasm or non-invasive coronary flow reserve assessment via echocardiographic Doppler, cardiac magnetic resonance imaging, or positron emission tomography.¹⁷

These guidelines and consensus statements reflect the increasing clinical interest in INOCA and the endorsement by professional societies of the importance of diagnosing these disorders.

Conclusion

This comprehensive review has discussed the key interrogative questions relating to patient management of INOCA (fig 1). Accordingly, along

with other recent authoritative papers,^{1 108 147 148} it provides the current evidence base to facilitate the diagnosis and management of these often neglected disorders. The future challenge is to implement what we already know concerning the diagnosis of INOCA and to expand the effectiveness of available treatments by personalising their use to the individual patient endotype.

The methods required to diagnose INOCA are well established and strongly advocated for in recent consensus statements^{1 147 148} and guidelines.¹⁰⁸ However, even in specialised centres proficient with functional coronary angiography techniques, few patients (<10%) with chest pain and non-obstructive coronary arteries undergo routine evaluation for a functional coronary cause of their symptoms. Therefore, change management principles are required to implement the more appropriate use of functional coronary angiography, considering that more than half of elective angiograms do not have obstructive coronary artery disease to account for their presenting symptoms. Achieving this practice change will require increasing awareness of these disorders by the continued advocacy of professional cardiology societies and dedicated medical societies (eg, COVADIS, <https://covadis.online/>), as well as consumer involvement via patient support groups (eg, INOCA International, <https://www.inocainternational.com/>; International Heart Spasm Alliance, <https://www.internationalheartspasmsalliance.org/>).

Implementation of routine functional coronary angiography in patients with INOCA will also encourage personalised treatment. INOCA is a heterogeneous disorder and the importance of delineating vasospastic angina and coronary microvascular disorders has been described. However, coronary microvascular disorders have multiple mechanisms, including different coronary pathophysiology producing myocardial ischaemia, as well as disturbances in nociception. With well characterised cohorts of patients with INOCA (that is, clinical and pathophysiological characteristics), the individual treatments that patients are more

PATIENT INVOLVEMENT

The manuscript was provided to two female patients with coronary vasomotor disorders who founded the International Heart Spasm Alliance. The patients expressed the need for earlier diagnosis and more recognition in the medical community and advocated for a holistic approach to assessment and management. Based on their reviews, the manuscript was modified to emphasise challenges and opportunities in current practice, such as the lack of clinical trial data for cardioprotective agents, minimising the impact on mental wellbeing, the usefulness of care plans for recurrent hospital admissions, and the role of multidisciplinary approaches including exercise training and chronic pain management.

Questions for future research

- Do cardioprotective treatments such as aspirin and statins reduce major adverse cardiovascular events in patients with ischaemia with non-obstructive coronary arteries (INOCA)?
- How can a standardised angina collection tool be implemented as a standard of care practice?
- What are the clinical outcomes of different INOCA subtypes? Contributors: DJ, RT, CZ, and JB conducted a review of the literature and prepared the manuscript draft. All authors were substantially involved in the conception, drafting, and editing of the manuscript. All authors have given final approval of the manuscript and are accountable for all portions of the manuscript. JB is the guarantor.

likely to respond to can be identified, which would be preferable to the trial-and-error approach currently used by clinicians. It would also provide a productive environment for the assessment of new INOCA treatments to improve the outcomes of these disorders.

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