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 ≥50%) should be diagnosed with INOCA (ischaemia with non-obstructive coronary arteries). 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 quantify 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 quantify 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
**Why treat?**

Chest pain with non-obstructive coronary arteries
- Increased risk of major adverse cardiac events (MACE)
- Impaired health status

**Who to treat?**

Ischaemia with non-obstructive coronary arteries (INOCA)
1. Establish INOCA diagnosis:
   - Exclude non-cardiac causes
   - Exclude non-ischaemic causes
2. Evaluate pathophysiological mechanisms (functional angiography):
   - Coronary macrovascular dysfunction (vasospastic angina)
   - Coronary microvascular dysfunction (coronary microvascular disorders)

**What are the treatment targets?**

INOCA treatment targets
1. Prognostic target — reducing the risk of MACE (cardioprotective treatments)
2. Health status target — reducing angina symptoms (anti-anginal treatments)
   - Anti-ischaemic treatments (pharmacological and non-pharmacological)
   - Anti-nociceptive treatments (pharmacological and non-pharmacological)

**How to treat?**

INOCA personalised medicine approach
1. Confirm pathophysiological mechanisms
   - Presence of ischaemia (that is, INOCA)
   - Macrovascular versus microvascular dysfunction
2. Avoid precipitating and aggravating factors
3. Cardioprotective treatments
4. Anti-anginal treatments
   - Vasospastic angina treatments
   - Coronary microvascular disorder treatments

**When to treat?**

Initiating INOCA treatment
1. At initial diagnosis — consider cardioprotective treatment (eg, vasospastic angina)
   - consider anti-anginal treatments if disabling symptoms
2. Clinical monitoring of health status — important because symptoms could fluctuate
3. Refractory angina — could require extensive anti-anginal treatments

**Where to next?**

Emerging treatments
1. Emerging pharmacological treatments — intense statin/angiotensin converting enzyme inhibitors, ticagrelor, zibotentan
2. Novel emerging treatments — *Rhodiola rosea*, CD34 stem cells, coronary sinus reducer

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. 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), threefold to fourfold increased risk of hospital admission, and hence a high healthcare cost burden 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 unslected 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.

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, with a subsequent extension study reporting that this proportion was slightly lower in Japanese patients than in white patients. 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. 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. 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). 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, which is a similar rate to those with obstructive coronary artery disease. Furthermore, about 15-25% of these patients are readmitted with chest pain or undergo repeat angiography (or both), thereby also affecting health resources. Moreover, compared with healthy controls, patients with chest pain and non-obstructive coronary arteries have a reduced quality of life at 12 months.

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.
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 “ankhone” 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 ≥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).

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

**Fig 3** | Common causes of chest pain in patients with non-obstructive coronary arteries. INOCA = ischaemia 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 CoRMINICA 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). The use of functional coronary angiography is further evident from other reports,5 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...
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. 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.

**Table 1 | Clinical attributes of INOCA coronary vasomotor disorders**

<table>
<thead>
<tr>
<th>Coronary microvascular disorders</th>
<th>Diagnostic investigation</th>
<th>Putative mechanism</th>
<th>Clinical presentation</th>
<th>Nitrate response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasospastic angina27</td>
<td>Spontaneous or inducible coronary artery spasm</td>
<td>Coronary artery spasm</td>
<td>Rest or unstable angina; smoking is a risk factor</td>
<td>Prompt</td>
</tr>
<tr>
<td>Coronary microvascular disorders24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac syndrome X</td>
<td>Positive stress ECG</td>
<td>Impaired microvascular vasodilation</td>
<td>Stable exertional angina; high prevalence in female patients</td>
<td>Limited</td>
</tr>
<tr>
<td>Microvascular angina</td>
<td>Impaired coronary flow reserve</td>
<td>Impaired microvascular vasodilation</td>
<td>Often rest angina; often female patients</td>
<td>Limited</td>
</tr>
<tr>
<td>Coronary slow flow phenomenon</td>
<td>Delayed vessel opacification on angiography</td>
<td>Increased microvascular resistance</td>
<td>Unstable angina; smoking is a risk factor</td>
<td>Variable</td>
</tr>
<tr>
<td>Microvascular spasm</td>
<td>Inducible pain and ischaemic ECG changes with acetylcholine, but no coronary artery spasm</td>
<td>Microvascular spasm</td>
<td>Unstable angina; often female patients</td>
<td>Variable</td>
</tr>
</tbody>
</table>

EKG=electrocardiogram.

**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.

**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.

**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.19

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 nifedipine,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-3,37 and phosphodiesterase-5 inhibitors, rho kinase inhibitors,36 97 angiotensin converting enzyme inhibitors72 and estradiol54 as well as lifestyle risk factor modification87-91 (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 anti-depressants104 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...
Table 2 | Potential anti-anginal treatments for ischaemia with non-obstructive coronary arteries

<table>
<thead>
<tr>
<th>Anti-anginal treatment</th>
<th>Possible mechanisms and clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-ischaemic pharmacological treatments</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Beta blockers (eg, atenolol, metoprolol)</strong></td>
<td>Inhibit myocardial beta 1 receptors (to reduce heart rate and contractility)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers, non-dihydropyridine (eg, verapamil, diltiazem)</strong></td>
<td>Inhibit L calcium channels in myocardial cells to reduce heart rate and contractility in specialised</td>
</tr>
<tr>
<td><strong>Calcium channel blockers, dihydropyridine (eg nifedipine, amlodipine)</strong></td>
<td>Conducting tissue to reduce heart and in VSMCs leading to vasodilation</td>
</tr>
<tr>
<td><strong>Long acting nitrates (eg, isosorbide dinitrate, isosorbide mononitrate)</strong></td>
<td>Increase nitric oxide release (to increase cGMP levels in VSMCs, leading to vasodilation), more potent</td>
</tr>
<tr>
<td><strong>Potassium channel activator (eg, nicorandil)</strong></td>
<td>Open VSMC potassium ATP channels (leading to vasodilation); increase nitric oxide release (to increase</td>
</tr>
<tr>
<td><strong>Late sodium current blockers (eg, ranolazine)</strong></td>
<td>cGMP levels in VSMCs (leading to vasodilation); balanced vasodilator in veins and arteries; epidermical</td>
</tr>
<tr>
<td><strong>Fatty acid oxidation inhibitors (eg, trimetazidine)</strong></td>
<td>Shift cardiac metabolism from fatty acid oxidation to glucose oxidation (to reduce myocardial oxygen</td>
</tr>
<tr>
<td><strong>Sinus node inhibitors (eg, ibabradine)</strong></td>
<td>Inhibit sinoatrial node I; current (to reduce heart rate)</td>
</tr>
<tr>
<td><strong>Angiotensin converting enzyme inhibitors (eg, enalapril)</strong></td>
<td>Inhibit conversion of angiotensin I to II (leading to vasodilation)</td>
</tr>
<tr>
<td><strong>Phosphodiesterase-3 inhibitors (eg, cilostazol)</strong></td>
<td>Increase cAMP levels in VSMCs (leading to vasodilation)</td>
</tr>
<tr>
<td><strong>Phosphodiesterase-5 inhibitors (eg, sildenafil)</strong></td>
<td>Increase cGMP levels in VSMCs (leading to vasodilation); caution with nitrates owing to increased cGMP</td>
</tr>
<tr>
<td><strong>Rho kinase inhibitors (eg, fasudil)</strong></td>
<td>Inhibit VSMC rho kinase (to increase MLC dephosphorylation, leading to vasodilation)</td>
</tr>
<tr>
<td><strong>Statins (eg, pravastatin, fluvastatin)</strong></td>
<td>Increase endothelial nitric oxide release (to increase cGMP levels in VSMCs, leading to vasodilation);</td>
</tr>
<tr>
<td><strong>Anti-ischaemic non-pharmacological treatments</strong></td>
<td>inhibit rho kinase pathway in VSMCs (to increase DLC phospholylation, leading to vasodilation)</td>
</tr>
<tr>
<td><strong>Stellate ganglion block</strong></td>
<td>Reduces cardiac sympathetic tone (to reduce vasoconstriction); disrupts cardiac sympathetic pain</td>
</tr>
<tr>
<td><strong>External counterpulsation</strong></td>
<td>Promotes retrograde aortic diastolic coronary flow (to increase coronary perfusion); reduces left</td>
</tr>
<tr>
<td><strong>Coronary sinus reducer</strong></td>
<td>Increases coronary venous pressure (leading to arterial dilation and increased perfusion)</td>
</tr>
<tr>
<td><strong>Anti-nociceptive targets</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants (eg, imipramine)</strong></td>
<td>Block noradrenaline reuptake (to inhibit pain modulating neurons, and reduce pain)</td>
</tr>
<tr>
<td><strong>Methylxanthines (eg, theophylline)</strong></td>
<td>Inhibit adenosine A1 receptor (to reduce pain)</td>
</tr>
<tr>
<td><strong>Opiates</strong></td>
<td>Activate dorsal root ganglia and peripheral nerve opioid receptors (to reduce pain)</td>
</tr>
<tr>
<td><strong>TENS unit</strong></td>
<td>Transcutaneous electrical nerve stimulus (to block pain afferents (gate theory))</td>
</tr>
<tr>
<td><strong>Spinal stimulator</strong></td>
<td>Spinal cord stimulation (C7 / T1 / T2 / T3; to block pain afferents (gate theory))</td>
</tr>
</tbody>
</table>

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 gastroesophageal 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Coronary microvascular dysfunction</th>
<th>Study design</th>
<th>Impact on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heugler (1979) 54</td>
<td>8</td>
<td>Nifedipine</td>
<td>Rest angina, NOCA, transient STE</td>
<td>Bedside test</td>
<td>Observational, non-randomised</td>
<td>Nifedipine reduced mean monthly angina episodes from 104 to eight</td>
</tr>
<tr>
<td>Ascherman (1990) 56</td>
<td>17</td>
<td>Nifedipine</td>
<td>Angina, NOCA, transient STE</td>
<td>Spontaneous spasm on angiography</td>
<td>Double blind, comparative crossover RCT</td>
<td>Nifedipine reduced mean weekly angina episodes from 43 to eight, after six weeks (P&lt;0.001)</td>
</tr>
<tr>
<td>Chahine (1993) 57</td>
<td>52</td>
<td>Amitriptyline</td>
<td>Angina, transient STE</td>
<td>Provoked spasm on angiography or beside</td>
<td>Double blind, placebo controlled, crossover RCT</td>
<td>Amitriptyline reduced mean daily angina episodes by 55% (placebo=15%) at four weeks (P=0.009)</td>
</tr>
<tr>
<td>Higuma (2010) 58</td>
<td>37</td>
<td>Nifedipine CR, diltiazem R</td>
<td>Angina, NOCA, ischaemic ECG</td>
<td>Provoked spasm on angiography</td>
<td>Open label, comparative RCT</td>
<td>Mean weekly angina episodes reduced over 12 weeks for nifedipine (2.6 to 0.4, P&lt;0.05) and diltiazem (2.7 to 0.3, P&lt;0.05)</td>
</tr>
<tr>
<td>Okawa (2010) 59</td>
<td>30</td>
<td>Nifedipine; bendipine</td>
<td>Angina, NOCA, ischaemic ECG</td>
<td>Provoked spasm on angiography</td>
<td>Comparative RCT</td>
<td>Nifedipine reduced mean weekly angina episodes from 3.5 (SD±2.7) to 0 (0-2), at eight weeks (P&lt;0.001); bendipine did not improve angina episodes (1.4 (±1.1) to 0.6 (±0.8), P&lt;0.05)</td>
</tr>
<tr>
<td>Kook (2020) 60</td>
<td>48</td>
<td>Diltiazem; nebivolol</td>
<td>Rest angina, NOCA</td>
<td>Provoked spasm on angiography</td>
<td>Double blind, parallel group RCT</td>
<td>Change (%) in diameter from baseline acetylcholine provocation test. Suppression of acetylcholine constriction: diltiazem (68 ±13%), nebivolol (50 ±8%) and nifedipine (47 ±12%) at 12 weeks (P&lt;0.05); SAQ scores improved in overall study population (80.3 ±7.9 to 85.4 ±7.8, P&lt;0.001); no significant difference in SAQ between diltiazem and nebivolol</td>
</tr>
<tr>
<td>β adrenergic agents</td>
<td></td>
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<tr>
<td>Shimizu (1993) 61</td>
<td>10</td>
<td>Denopamine</td>
<td>Rest angina, NOCA, ischaemic ECG</td>
<td>Provoked spasm on angiography</td>
<td>Placebo controlled RCT</td>
<td>Denopamine reduced mean daily angina frequency compared with placebo (0.6 (SD±1.2) v 2.2 (±1.3), P&lt;0.005)</td>
</tr>
<tr>
<td>Long acting nitrates</td>
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<tr>
<td>Ascherman (1990) 62</td>
<td>17</td>
<td>Isosorbide dinitrate</td>
<td>Angina, NOCA, transient STE</td>
<td>Spontaneous spasm on angiography</td>
<td>Double blind, comparative, crossover RCT</td>
<td>Isosorbide dinitrate reduced mean weekly angina episodes from 43 to four, after six weeks (P&lt;0.001)</td>
</tr>
<tr>
<td>Potassium channel openers</td>
<td></td>
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<tr>
<td>Kishida (1987) 63</td>
<td>32</td>
<td>Nicorandil</td>
<td>Angina, NOCA, transient STE</td>
<td>NA</td>
<td>Single blind, placebo controlled, crossover RCT</td>
<td>Nicorandil reduced mean daily angina episodes compared to placebo (placebo=mean 3.6 (SE±0.4) per day, nicorandil=0.7 (±0.2) per day, P&lt;0.001)</td>
</tr>
<tr>
<td>Lablanche (1992) 64</td>
<td>13</td>
<td>Nicorandil; nifedipine</td>
<td>Angina, NOCA, transient STE</td>
<td>Spontaneous or provoked spasm on angiography</td>
<td>Single blind, placebo controlled, crossover RCT</td>
<td>Nicorandil suppressed inducible spasm in 92% of patients (all inducible on placebo), nifedipine suppressed inducible spasm in 69% of patients (all inducible on placebo)</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
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<tr>
<td>Yasue (2008) 65</td>
<td>64</td>
<td>Fluvastatin</td>
<td>Angina, NOCA, positive stress test, background CCB treatment</td>
<td>Acetylcholine induced spasm on angiography</td>
<td>Open label RCT</td>
<td>75% of patients in the fluvastatin group became asymptomatic after 6 months (P&lt;0.001), compared to 70% of control patients (P&lt;0.001)</td>
</tr>
<tr>
<td>Kim (2019) 66</td>
<td>100</td>
<td>Atorvastatin; sarpogrelate</td>
<td>Chest pain, NOCA, substantial ST-T wave change</td>
<td>Provoked spasm on angiography</td>
<td>Placebo controlled RCT with 2+2 design</td>
<td>Atorvastatin and sarpogrelate did not affect readmission rate compared with placebo (sarpogrelate + atorvastatin 47%, sarpogrelate 58%, atorvastatin 40% and placebo 56%, P=0.74)</td>
</tr>
<tr>
<td>Oestrogens</td>
<td></td>
<td></td>
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<tr>
<td>Kawano (2001) 67</td>
<td>15</td>
<td>17β oestradiol</td>
<td>Rest angina, NOCA, transient STE elevation</td>
<td>Provoked spasm on angiography</td>
<td>Placebo controlled RCT</td>
<td>17β oestradiol suppressed hyperventilation induced angina in all patients on the third day of supplementation</td>
</tr>
<tr>
<td>Exercise therapy or lifestyle</td>
<td></td>
<td></td>
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<tr>
<td>Morikawa (2013) 68</td>
<td>26</td>
<td>Exercise training</td>
<td>Rest angina, NOCA, ischaemic ECG</td>
<td>Provoked spasm on angiography</td>
<td>Non-randomised intervention</td>
<td>Exercise training improved median angina episodes from 2 (IQR 1-7) to 0 (0-2) at five days (P&lt;0.001)</td>
</tr>
<tr>
<td>Novel agents</td>
<td></td>
<td></td>
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<tr>
<td>Huckell (1981) 69</td>
<td>18</td>
<td>Perhexiline</td>
<td>Rest angina, STE</td>
<td>Transient ST elevation, spasm on angiography in 13</td>
<td>Non-randomised interventions</td>
<td>Perhexiline reduced angina episodes</td>
</tr>
<tr>
<td>Morita (2014) 70</td>
<td>73</td>
<td>Pioglitazone</td>
<td>Rest angina, NOCA, ischaemic ECG, background CCB treatment</td>
<td>Acetylcholine induced spasm on angiography</td>
<td>Open label RCT</td>
<td>Pioglitazone improved angina episodes by 75% but was not different compared to placebo (74%, P&lt;0.001) at six months</td>
</tr>
<tr>
<td>Shin (2014) 71</td>
<td>50</td>
<td>Cilostazol</td>
<td>Chest pain, NOCA, ischaemic ECG, background CCB treatment</td>
<td>Provoked spasm on angiography</td>
<td>Double blind, placebo controlled, RCT</td>
<td>Cilostazol reduced weekly angina episodes (mean 66 (SD±87%) compared to placebo (18±140%, P&lt;0.009) at six months</td>
</tr>
</tbody>
</table>

NOCA=non-obstructive coronary arteries; NCA=normal coronary arteries; STE=segment elevation; RCT=randomised clinical trial; CFR=coronary flow reserve; CSPS=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=intertquartile range.
Table 4 | Coronary microvascular disorder studies

<table>
<thead>
<tr>
<th>Calcium channel blockers</th>
<th>No</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Coronary microvascular dysfunction</th>
<th>Study design</th>
<th>Impact on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannon (1985)†</td>
<td>26</td>
<td>Verapamil; nifedipine</td>
<td>Chest pain, NCA</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled, crossover RCT</td>
<td>CCBs improved angina episodes compared to placebo (mean 21 SD±21 v 35±27, P&lt;0.001)</td>
</tr>
<tr>
<td>Cannon (1990)†</td>
<td>11</td>
<td>Lidoflazine</td>
<td>Chest pain, NCA</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled, RCT</td>
<td>Lidoflazine did not affect angina episodes (mean −9 SD±7, P&gt;0.05) at seven weeks</td>
</tr>
<tr>
<td>Beltrame (2004)†</td>
<td>20</td>
<td>Mibefradil</td>
<td>Angina, NOCA</td>
<td>CSFP</td>
<td>Double blind, placebo controlled, crossover RCT</td>
<td>Mibefradil reduced monthly angina episodes by 56% compared to placebo (P&lt;0.001)</td>
</tr>
<tr>
<td>Zhang (2014)†</td>
<td>66</td>
<td>Diltiazem; fluvasatin</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Randomised trial</td>
<td>Diltiazem + fluvasatin improved mean exercise time at 90 days compared to either drug alone (mean 446 SD±164 v 250±104 seconds, P&lt;0.05)</td>
</tr>
<tr>
<td>Beta adrenergic agents</td>
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<tr>
<td>Lanza (1999)†</td>
<td>10</td>
<td>Atenolol, amiodipine; isosorbide mononitrate</td>
<td>Exercise angina, NCA, positive stress test</td>
<td>Not assessed</td>
<td>Double blind, placebo controlled, comparative RCT</td>
<td>Atenolol reduced monthly angina episodes from mean 24 (SD±18) to 15 (±13, P&lt;0.05), amiodipine and isosorbide mononitrate had no impact on angina episodes</td>
</tr>
<tr>
<td>Sen (2009)†</td>
<td>38</td>
<td>Nebivolol; metoprolol</td>
<td>Angina, NCA, transient ST depression during exercise</td>
<td>Not required</td>
<td>Single blind RCT</td>
<td>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</td>
</tr>
<tr>
<td>Long acting nitrates</td>
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<tr>
<td>Bugiardini (1993)†</td>
<td>16</td>
<td>Isosorbide dinitrate</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Isosorbide dinitrate decreased time to angina on exercise testing compared to baseline (mean 477 SD±93 v 561±108 seconds, P&lt;0.002)</td>
</tr>
<tr>
<td>Russo (2013)†</td>
<td>29</td>
<td>Isosorbide dinitrate</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Isosorbide dinitrate did not affect exercise duration</td>
</tr>
<tr>
<td>Potassium channel openers</td>
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<tr>
<td>Yamabe (1995)†</td>
<td>11</td>
<td>Nicorandil</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Nicorandil improved the extent of ischaemia score on 201Thallium scintigraphy (before, mean 0.37 SD±0.22; after, 0.20±0.15, P&lt;0.05)</td>
</tr>
<tr>
<td>Chen (1997)†</td>
<td>13</td>
<td>Nicorandil</td>
<td>Angina, NCA, positive stress test</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled, crossover RCT</td>
<td>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</td>
</tr>
<tr>
<td>Statins</td>
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</tr>
<tr>
<td>Kayikcioglu (2003)†</td>
<td>40</td>
<td>Pravastatin</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Single blind, placebo controlled RCT</td>
<td>Pravastatin improved mean exercise time (mean 530 SD±162 v 585±165 seconds, P&lt;0.05) and time to 1 mm ST depression (267±105 v 419±162 seconds, P&lt;0.05) at 90 days</td>
</tr>
<tr>
<td>Fabian (2004)†</td>
<td>40</td>
<td>Simvastatin</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Open label, placebo controlled RCT</td>
<td>Simvastatin improved time to 1 mm ST depression (mean 4.45 SD±0.39 v 5.33±0.27 minutes, P&lt;0.001) at 12 weeks, but was unchanged with placebo</td>
</tr>
<tr>
<td>Oestrogen</td>
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</tr>
<tr>
<td>Bairey Merz (2010)†</td>
<td>35</td>
<td>Norethindrone or ethinyl estradiol</td>
<td>Angina, NOCA, positive stress test</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled RCT</td>
<td>Oestrogen treatment increased angina-free status compared to placebo (41% v 22% angina free, P=0.02) at 12 weeks</td>
</tr>
<tr>
<td>Renin/angiotensin/aldosterone inhibitors</td>
<td></td>
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<tr>
<td>Kaski (1994)†</td>
<td>19</td>
<td>Enalapril</td>
<td>Angina, NCA, positive stress test</td>
<td>Abnormal CFR</td>
<td>Single blind, placebo controlled, crossover RCT</td>
<td>Enalapril improved total exercise time (mean 779 SD±141 v 690±148 seconds, P=0.006) at two weeks</td>
</tr>
<tr>
<td>Motz (1996)†</td>
<td>15</td>
<td>Enalapril</td>
<td>NCA, abnormal resting ECG or positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Enalapril improved CCS angina class (mean 2.5 SD±0.6 to 1.5 SD±0.4, P&lt;0.01) at 12 months</td>
</tr>
<tr>
<td>Chen (2002)†</td>
<td>20</td>
<td>Enalapril</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Double blind, placebo controlled RCT</td>
<td>Enalapril reduced weekly angina episodes (mean 1.6 SD±0.5 v 0.5±0.4, P&lt;0.05) at eight weeks</td>
</tr>
<tr>
<td>Pauly (2011)†</td>
<td>78</td>
<td>Quinapril</td>
<td>Angina, NOCA</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled RCT</td>
<td>Quinapril reduced angina episodes at 16 weeks compared to placebo (P=0.037)</td>
</tr>
<tr>
<td>Bavry (2014)†</td>
<td>41</td>
<td>Eplerenone</td>
<td>Angina, NCA, positive stress test</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled RCT</td>
<td>Eplerenone did not affect angina episodes at 16 weeks, compared with placebo</td>
</tr>
<tr>
<td>Michelsen (2018)†</td>
<td>63</td>
<td>Ramipril</td>
<td>Angina, NCA, not required</td>
<td>Abnormal CFR</td>
<td>Double blind, placebo controlled RCT</td>
<td>Ramipril did not affect angina episodes at 24 weeks, compared with placebo</td>
</tr>
<tr>
<td>Nitric oxide modifiers</td>
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<tr>
<td>Lerman (1998)†</td>
<td>26</td>
<td>L-arginine infusion</td>
<td>Chest pain, NOCA</td>
<td>Not assessed</td>
<td>Double blind, placebo controlled RCT</td>
<td>L-arginine improved qualitative symptom scores compared with placebo (P&lt;0.05)</td>
</tr>
</tbody>
</table>

(Continued)
### Novel anti-anginal agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Coronary microvascular dysfunction</th>
<th>Study design</th>
<th>Impact on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vries (2007)</td>
<td>94</td>
<td>24</td>
<td>TENS/spinal cord stimulation</td>
<td>Angina, NCA, positive stress test</td>
<td>Not assessed</td>
<td>Double blind, placebo controlled RCT</td>
<td>Doxazosin did not affect exercise induced angina at 10 weeks</td>
</tr>
<tr>
<td>Luo (2012)</td>
<td>89</td>
<td>45</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Double blind, placebo controlled RCT</td>
<td>Doxazosin did not affect total exercise time or time to 1 mm ST depression compared to placebo, at seven days</td>
<td></td>
</tr>
</tbody>
</table>

### Exercise therapy or lifestyle factors

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Coronary microvascular dysfunction</th>
<th>Study design</th>
<th>Impact on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson (2000)</td>
<td>86</td>
<td>26</td>
<td>Exercise training</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Parallel design (usual care) RCT</td>
<td>Exercise training improved time to angina relative to baseline (mean 4 SD±1 661 minutes, P=0.01)</td>
</tr>
<tr>
<td>Tylin-Lenne (2002)</td>
<td>87</td>
<td>28</td>
<td>Exercise training</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Parallel design (usual care) RCT</td>
<td>Exercise training improved walk distance relative to baseline (mean 535 SD±47 x 587±49 metres, P=0.006)</td>
</tr>
<tr>
<td>Asbury (2008)</td>
<td>88</td>
<td>28</td>
<td>Cardiac rehabilitation</td>
<td>Chest pain, NCA, positive stress test</td>
<td>Not required</td>
<td>Parallel design (usual care) RCT</td>
<td>Cardiac rehabilitation improved symptom severity at eight weeks (before, mean 2.0 SD±0.8 after 1.26±1.1, P=0.009)</td>
</tr>
<tr>
<td>Feizl (2012)</td>
<td>89</td>
<td>30</td>
<td>Cardiac rehabilitation</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Parallel design (usual care) RCT</td>
<td>Cardiac rehabilitation improved physical functioning scores compared to controls (mean 59 SD±8 x 36±13, P=0.05)</td>
</tr>
<tr>
<td>Feizl (2012)</td>
<td>11</td>
<td>40</td>
<td>Relaxation therapy</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Parallel design (usual care) RCT</td>
<td>Relaxation therapy improved physical functioning scores compared to controls (mean 51 SD±13 x 30±9, P=0.05)</td>
</tr>
<tr>
<td>de Carvalho (2015)</td>
<td>92</td>
<td>12</td>
<td>Exercise training</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Exercise training improved physical functioning scores relative to baseline (mean 88 SD±9 x 45±26, P=0.001)</td>
</tr>
<tr>
<td>Sos (2015)</td>
<td>93</td>
<td>24</td>
<td>Cardiac rehabilitation</td>
<td>Angina, NCA, positive stress test</td>
<td>Not required</td>
<td>Non-randomised intervention</td>
<td>Cardiac rehabilitation improved exercise duration of exercise relative to baseline (mean 760 SD±142 x 636±157 seconds, P=0.001)</td>
</tr>
<tr>
<td>Bove (2020)</td>
<td>94</td>
<td>45</td>
<td>Exercise and risk factor control</td>
<td>Angina, NOCA</td>
<td>Abnormal CFR</td>
<td>Parallel design (usual care) RCT</td>
<td>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)</td>
</tr>
</tbody>
</table>

### Devices

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>Intervention</th>
<th>Inclusion criteria</th>
<th>Coronary microvascular dysfunction</th>
<th>Study design</th>
<th>Impact on outcomes</th>
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</thead>
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<td>Ellasson (1993)</td>
<td>95</td>
<td>12</td>
<td>Spinal cord stimulation</td>
<td>Angina, NCA, positive stress test</td>
<td>Not assessed</td>
<td>Non-randomised intervention</td>
<td>Spinal cord stimulation improves exercise test time to angina (before 2.7 ±0.9, 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)</td>
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<td>Jessurun (2003)</td>
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<td>8</td>
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<td>Angina, NCA, positive stress test</td>
<td>Not assessed</td>
<td>Non-randomised intervention</td>
<td>TENS reduced angina episodes at four weeks relative to baseline (mean 20.5 SD±3 x 31±, P=0.01)</td>
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<tr>
<td>De Vries (2007)</td>
<td>97</td>
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<td>Luo (2012)</td>
<td>98</td>
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<td>Non-randomised intervention</td>
<td>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)</td>
</tr>
</tbody>
</table>

**Notes:** NOCA=non-obstructive coronary arteries; NCA=normal coronary arteries; STE=ST segment elevation; RCT=randomised clinical trial; CFR=coronary flow reserve; CSFP=coronary flow phenomemon; SAQ=Seattle Angina Questionnaire; W0=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.
in women. Patients with microvascular angina can experience rest angina, atypical symptoms, or episodes triggered by emotional stress. 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, where its cessation is strongly recommended.

### Sympathomimetic agents

These agents include the recreational use of cocaine, methamphetamines (ice), and methylenedioxy-N-methamphetamine (ecstasy), all of which could precipitate vasospastic angina episodes. In addition, therapeutically used sympathomimetic agents (adrenaline, noradrenaline, dopamine).
noradrenaline, and methylphenidate\textsuperscript{115}) 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.\textsuperscript{116} In contrast, beta blockers have been reported to improve angina in patients with coronary microvascular dysfunction\textsuperscript{35}; reflecting the importance in delineating the different pathophysiological mechanisms.

**Other drug treatments**
Ergot alkaloids\textsuperscript{117} and serotonin\textsuperscript{118} have been used as provocative stimuli in spasm testing. Hence ergot preparations used in the treatment of migraine\textsuperscript{119} or uterine bleeding\textsuperscript{120} and serotonin uptake inhibitors used in treating depression\textsuperscript{121} could precipitate coronary spasm. Some chemotherapy agents (5-flurouracil,\textsuperscript{122} capecitabine,\textsuperscript{123} sorafenib\textsuperscript{124}) have also been described to precipitate episodes of vasospastic angina. General anaesthesia has been associated with inducing coronary spasm,\textsuperscript{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,\textsuperscript{126} coronary microvascular dysfunction,\textsuperscript{127} myocardial ischaemia,\textsuperscript{128, 129} and angina\textsuperscript{127} 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,\textsuperscript{130-133} as well as depression.\textsuperscript{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,\textsuperscript{37} and their cessation is associated with an increased risk of MACE.\textsuperscript{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.\textsuperscript{136} 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.\textsuperscript{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,\textsuperscript{106} and these treatments are the focus of a large prospective clinical trial that is in progress.\textsuperscript{138}

**Anti-anginal treatments**

**Vasospastic angina**
In addition to cardioprotective benefits, calcium channel blockers are effective at reducing angina symptoms in these patients.\textsuperscript{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 nitrates;\textsuperscript{21} however, as stated above, their benefits have recently been questioned.\textsuperscript{134} Other novel agents with clinical randomised controlled trial data supporting their use as anti-anginal agents in vasospastic angina include nicorandil\textsuperscript{61, 62} and cilostazol\textsuperscript{57} (table 3). In addition, aerobic exercise training has been shown to reduce angina episodes in patients with vasospastic angina.\textsuperscript{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 flow\textsuperscript{63} 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—
- Ischaemia (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 and increased exercise capacity.85-87

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 figu 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.
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. 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 (P2) platelet receptors to exert an anti-platelet effect. The raised endogenous adenosine levels also stimulate the purinergic 1 (P1) receptors, which includes the A2A receptor, resulting in coronary microvascular vasodilatation. 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. 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. 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. 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, as has a recent preliminary study in patients with INOCA. 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. 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 syndromes 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. 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.

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, 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 and guidelines. 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.com/), 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 likely to benefit from can be identified.

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 without obstructive coronary artery disease (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 provide a productive environment for the assessment of new INOCA treatments to improve the outcomes of these disorders.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

9. Rumsfeld JS. Health status and clinical practice: when will they meet? Circulation 2002;106:5-7. doi:10.1161/01.CIR.106.6.5


O’Connor FM, Robinson WE. Enhanced external counterpulsation is an effective treatment for Syndrome X. Int J Cardiol 2009;357:256-7. doi:10.1016/j.ijcard.2008.03.022


STATE OF THE ART REVIEW


