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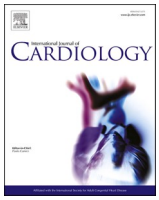

Clinical standards in angina and non-obstructive coronary arteries: A clinician and patient consensus statement

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ABSTRACT

Patients with angina and non-obstructive coronary arteries (ANOCA) or myocardial ischaemia with non-obstructive coronary arteries (INOCA) comprise a relatively large subgroup within those with ischaemic heart disease.

Advances in the understanding of disease mechanisms, diagnostic tests and multidisciplinary care are improving awareness of the needs of affected individuals. However, practice variations and suboptimal management promulgate the health burden and increase health care resource consumption.

Clinical standards represent a limited number of quality statements that describe the care patients should be offered by health professionals and providers for a specific clinical condition or defined clinical pathway in line with current best evidence. Clinical standards should address implementation of this evidence along with education of patients and healthcare professionals, multidisciplinary care networks, and research.

In this consensus statement, we highlight contemporary evidence and stakeholder views, including clinicians and patients, to provide an international perspective for developing clinical standards for services involving ANOCA/INOCA patients. A clinical service for ANOCA/INOCA should "consider the whole patient" and provide a multidisciplinary, patient-centred service.

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1. Introduction

1.1. Nomenclature and epidemiology

Chronic, stable ischaemic heart disease includes two major overlapping subgroups: angina and non-obstructive coronary arteries (ANOCA) and ischaemia with non-obstructive coronary arteries (INOCA) [1,2]. The term "ANOCA" originated from a COVADIS Summit and the term "INOCA" was introduced in 2017 by a National Heart, Lung, and Blood Institute workshop [3] to identify patients with myocardial ischaemia triggered by mechanisms other than obstructive epicardial coronary artery disease. More recently, Boden and colleagues have proposed 'myocardial ischaemic syndromes' [4] as an inclusive term for ANOCA/INOCA and atherosclerotic coronary artery disease.

In 2019, global estimates for ischaemic heart disease included 197.2 million (95 % UI: 177.7 to 219.5) prevalent cases, 9.1 million (95 % UI: 8.4 to 9.7) deaths, and 182.0 million (95 % UI: 170.2 to 193.5) disability-adjusted life years relating to ischaemic heart disease [5]. Angina is a frequent reason for attending primary care [6]. However, in stable chest pain populations, obstructive atherosclerotic coronary artery disease is identified only in a minority (10.7–25.7 %) of patients [7–9]. Therefore, most patients presenting with stable angina have non-obstructive coronary artery disease or so-called angiographically "normal appearing" coronary arteries and around two in five of these patients may have ANOCA/INOCA [10]. However, in patients with abnormal coronary vasoconstriction noninvasive diagnostic testing may be normal, hence the true prevalence may be higher. Prospective studies in patients with stable ischaemic heart disease referred for coronary angiography revealed that, based on functional coronary testing, the number of patients with non-obstructive causes of ischaemia outnumber those with flow-limiting coronary stenoses [11].

1.2. What are the ANOCA/INOCA endotypes?

Coronary artery spasm and microvascular dysfunction/disease are distinct and overlapping vascular disorders that may cause anginal symptoms [11–13]. The definitions of microvascular angina and vasospastic angina are described in the Supplement [14–16]. Spasm may involve the epicardial coronary artery and/or the microcirculation [17–22].

1.3. ANOCA/INOCA management

Clinical guidelines have established evidence-based recommendations for the diagnosis and management of ANOCA/INOCA (Supplement, Table S1) [1,2]. Emerging clinical evidence [20–31] and scientific consensus statements for ANOCA/INOCA [32] support the rationale for defining clinical care [33] and quality standards [34,35], as is the case for other medical conditions.

2. Clinical standards for ANOCA/INOCA

2.1. What are clinical and quality standards and indicators?

Clinical standards provide a framework for delivering appropriate care and reducing unwarranted variation [33]. They represent a limited number of quality statements that describe the care patients should be offered by health professionals and providers for a specific clinical condition or defined clinical pathway in line with current best evidence. Clinical standards should address implementation of this evidence along with education of patients and healthcare professionals, multidisciplinary care networks, and research. They define the care people can expect to be offered or receive for a specific clinical condition or defined clinical pathway in line with best evidence, considering the total patient, regardless of their age, sex, ethnicity, or socio-economic background [34].

Quality standards include clinical and non-clinical areas identified with variations in practice [34]. Indicators measure outcomes that reflect the quality of care, or processes linked by evidence to improved outcomes [35]. Quality statements, informed by established evidence, serve as benchmark criteria for measuring healthcare and for improvement based on an action plan with monitoring of delivery [34,35].

2.2. Are clinical standards warranted for ANOCA/INOCA?

Currently, gaps in clinical care pathways for ANOCA/INOCA may result in unwarranted variation in care, adding to the health burden for patients [21–28], who repeatedly attend primary and secondary care [24–28] [Fig. 1]. ANOCA/INOCA symptoms are associated with adverse physical, mental, social, and health-related quality of life [29,30]. Patients with ANOCA/INOCA have reported frequent time missed from work [29,31], suggesting a substantial economic impact [31,36]. Overall, the main cause of cardiovascular morbidity is angina and related episodes of care [24–28].

Advances in the understanding of disease mechanisms, diagnostics and clinical strategies provide new opportunities for optimizing the management and outcomes of patients with ANOCA/INOCA, as outlined in the guidelines (Table S1). On the other hand, lack of access, heterogeneity in practice and suboptimal management promulgate the health burden, potentially leading to avoidable episodes of medical care. Diagnostic criteria are established [1,2,14–16] and contemporary clinical guidelines describe algorithms for patients with suspected ANOCA/INOCA [1,2]. The care needs of affected individuals have been expressed through surveys [29,30]. ANOCA/INOCA is a global health problem [24–28,37] and the availability of care standards should help to facilitate standardization of healthcare implementation [38,39] and quality improvement internationally [40].

2.3. Development of clinical standards for ANOCA/INOCA

Accordingly, clinicians with relevant expertise and people with lived experience of ANOCA/INOCA have developed this manuscript [29]. Representative patient forums [41,42] and stakeholder guidance [15,16] have been consulted and the authors have worked together during 2022–2024 to generate an initial roadmap of clinical standards for ANOCA/INOCA (Tables 1 and S2). In the future, this framework is anticipated to evolve in line with clinical evidence and patient feedback. The key components for clinical service provision in ANOCA/INOCA are described. The document should represent a useful guideline for healthcare providers and patients. The plan is forward looking, anticipating repeated cycles of data collection through consultations and surveys, with an iterative approach towards healthcare improvement.

2.4. Clinical standards for ANOCA/INOCA: an initial framework

Ten standards are proposed for an ANOCA/INOCA clinical service (Table 1). The rationale draws upon clinical standards for health conditions in general and is also specific to ANOCA/INOCA. The goals for adoption include education, diagnostic services, treatment, multidisciplinary care, rehabilitation, a personalized care plan, community links, medical research, quality, and stakeholder engagement. These elements may be aspirational and achieving them should be goal-directed with a continuous cycle for improvement.

An ANOCA/INOCA service is optimized by multidisciplinary care and a hub-and-spoke model may be helpful. The hub should be the cardiology clinic, and the spokes should link to primary care, diagnostic and other secondary care services, allied health professionals (including cardiac rehabilitation which has a key role for implementation) [30,43], and social services. The format will vary according to the existing local frameworks of healthcare, reflecting variance in service provision in urban, remote, and rural areas [44,45]. In line with feedback from patients with lived experience, long distance travel for episodes of care,

Table 1
Clinical standards for INOCA.

Domain	Indicators
Education	Patients – Provision of information sheets and online resources presented in various formats including videos. Written word and easy read with visual support and the additional option of face-to-face contact for those who cannot access IT. Professionals – Education strategy and implementation
Diagnosis	Documentation of systemic health e.g., hemoglobin, renal function Anatomical imaging – Coronary angiography, non-invasive or invasive Functional imaging – Non-invasive nuclear or cardiovascular magnetic resonance imaging Invasive coronary function tests including acetylcholine in line with guidelines [2].
Management	Risk assessment including documentation of heart rate, blood pressure, body mass index, lipids, HbA1c, autoimmune disease, inflammatory disease. Patient-reported outcome measures Lifestyle interventions – Medical advice, community support groups, educational groups such as an expert patients Programme Medicines – Prescription of preventive therapy and angina therapy Healthcare professional training for INOCA
Managed care networks (multidisciplinary care)	Links between primary and secondary care Multidisciplinary secondary care – Cardiology, neurology, rehabilitation services, women's health services Social services – Links for welfare allowance, sickness benefit
Rehabilitation	Access to tailored cardiac rehabilitation – Local and/or online (specific for INOCA with knowledgeable staff)
Care plan	A personalized, patient centred, updatable care plan for the patient and carer. Monitoring – Return appointment(s) to assess the response to therapy and natural history
Community	Materials describing local, national and international patient forums, as well as patient led groups and initiatives.
Research	Healthcare professionals should have the option to be involved in research where possible. Every patient should be given the opportunity to participate in research
Quality	Audit - data capture framework (performance and outcome measures), and data collection to inform service planning, implement audit and clinical governance. Evidence of healthcare improvement.
Stakeholders	Evidence of links with stakeholder groups e.g., American Heart Association, British Heart Foundation, patient forums, patient groups, and patient led initiatives.

including for a caretaker or companion, should be supported.

2.4.1. Clinical audit

A clinical standard should be linked to a reference criterion, such as contemporary guideline recommendations (Table S1) [1,2], hence amenable to audit and healthcare improvement. Clinical standards can also be used to support accreditation. ICD-10 codes exist for ischaemic heart disease and are used for ANOCA/INOCA (e.g. I20.9).

3. Education

A clinical service for ANOCA/INOCA should have an education strategy for healthcare professionals and service users. A patient advocate with lived experience of ANOCA/INOCA is well placed to provide guidance, including if this person is or was a health care worker. Scoping an educational strategy can be informed by other established healthcare practices, such as the NHS Education for Scotland's principles of education planning [46]:

1. Promoting equality and diversity and tackling health inequalities
2. Working in partnership with stakeholders and demonstrating leadership
3. Enhancing digital access to learning, services, and information
4. Systematically planning our activities, measuring their impact, and learning from insights
5. Continually improving quality, and leading and harnessing innovation
6. Accountability for decisions, rooted in effective governance.

3.1. Education of healthcare professionals

Education underpins best practice. Incomplete knowledge of current medical evidence may lead to unwanted variation in practice. Educational programs for healthcare professionals face the challenge that ischaemic heart disease has been envisaged for decades as a stenosis-centred condition. Comprehensive, transformative educational programs addressing all professionals working with ischaemic heart disease patients, supported in meaningful clinical examples, are key to facilitate this change in thinking. Feedback from patients with lived experience of their condition will enhance knowledge and understanding by their healthcare professionals and will help to raise awareness [47]. An education program will also provide a mechanism to facilitate peer support and a "learn from each other" culture. Educational materials may include, for example, videos of patients' testimony of their experiences.

Healthcare professionals may benefit from a network for education, training, and leadership. An educational strategy within a healthcare or professional organization enhances awareness of new research evidence and translation of these findings into the clinic to improve patient care.

The implementation of an educational strategy can be achieved in a variety of ways. Education can be enabled by online meetings involving lectures, case-based discussions, knowledge exchange, and gap analyses. Studies showing how diagnosis and treatment plans in stable ischaemic heart disease are substantially modified on the grounds of objective evidence, such as obtained with functional coronary testing, stimulate new insights and adoption of new practices [11,12]. The educational value can be enhanced through contributions by professionals from diverse backgrounds, for example, primary and secondary care, women's health, cardiac rehabilitation, occupational therapy and pharmacy. Because clinical cardiologists initially review and later follow-up patients with stable ischaemic heart disease, they should understand the role of non-invasive tests to diagnose non-obstructive ischaemia, and the selected use of invasive tests of coronary vasomotor function in patients with refractory symptoms and/or reduced health-related quality of life, in line with a Class IB recommendation in clinical guidelines [2]. Requesting these investigations is an important factor in driving healthcare providers to adopt them.

3.2. Education of patients and care providers

Patients affected by ischaemic heart disease, including ANOCA/INOCA, should be provided with information about their condition in their native language. This information should include guidance on diagnosis, management, and prognosis. Highlighting local support networks, including welfare support, is also relevant. The information may include handouts, video display units in the outpatient waiting area, and website addresses, including to patient groups and forums [41,42,48,49] and to enhance the awareness of clinical guidelines [50] These resources can facilitate shared-care, self-management by patients and community rehabilitation.

4. Diagnostic management of ANOCA/INOCA

Detailed information on the diagnostic management of ANOCA/INOCA [50–60] is provided in the Supplement.

4.1. Lived experience of diagnosis

In a self-reported survey involving 297 patients with ANOCA/INOCA, 34.4 % were living with symptoms for three or more years before an ANOCA/INOCA diagnosis, and 77.8 % were told their symptoms were not cardiac [29]. Patients with ANOCA/INOCA present ad hoc during unselected care in general practice and hospital-based inpatient and outpatient care. The pathway to establish (rule-in or rule-out) a new diagnosis of ANOCA/INOCA should include a multidisciplinary approach, and a multidisciplinary team (MDT) meeting, with progress updates for individual patients.

4.2. Acute care triage

Emergency Medicine staff should be educated about ANOCA/INOCA. For example, patients may experience prolonged, severe chest pain, even in association with a normal electrocardiogram and/or a blood troponin concentration less than the sex-specific 99th centile. Given ANOCA/INOCA is a chronic condition, patients may know which treatments work best. Emergency Medicine staff should support this personalized care and facilitate triage for cardiology management as an inpatient or outpatient, as clinically appropriate.

4.3. Cardiology diagnostic management

A clinical service for ANOCA/INOCA should include access to non-invasive diagnostic imaging, an exercise ECG and invasive coronary function testing. To provide cost-efficient and equitable access to advanced diagnostic tests involving trained staff and expensive equipment, clinical services may be provided through regional healthcare networks. Patients with lived experience should be involved in the co-production of clinical care pathways, including educational materials with links to local forums and support services.

Non-invasive tests should be used initially (first-line) to assess for myocardial ischaemia (functional tests) and coronary artery disease (CT coronary angiography (CTCA) [2]. A pragmatic diagnostic approach for patients with suspected ANOCA involves first, undertaking CTCA to clarify coronary artery anatomy and disease, and then if obstructive coronary artery disease is excluded an exercise ECG can be useful to rule-in or rule-out inducible ischaemia in patients with ANOCA [59,60]. This strategy is useful to inform the diagnosis and treatment plan. Furthermore, the exercise ECG can be safely repeated to assess the functional response to treatment. Stress imaging by nuclear or MRI methods is also diagnostically useful to detect and quantify abnormalities in myocardial blood flow [2].

The reference method for the diagnostic evaluation of ischaemia secondary to coronary micro- or macrovascular spasm involves intracoronary administration of acetylcholine (an off-label indication) by an invasive cardiology team with relevant experience [1,2] (Supplement). The European guidelines state "*In persistently symptomatic patients despite medical treatment with suspected ANOCA/INOCA (i.e. anginal symptoms with normal coronary arteries or non-obstructive lesions at non-invasive imaging, or intermediate stenoses with normal FFR/iFR at coronary arteriography) and poor quality of life, invasive coronary functional testing is recommended to identify potentially treatable endotypes and to improve symptoms and quality of life, considering patient choices and preferences.*" [2] Information on the diagnostic management of ANOCA/INOCA is also available through patient forums [41,42] and stakeholder organizations [48,49].

5. Prognosis

Detailed information on prognosis is provided in the Supplement [55–58].

6. Treatment of ANOCA/INOCA

6.1. General approach

Medical therapy for ANOCA/INOCA is supported by guidelines [1,2], scientific consensus statements [31] and systematic reviews [59], and large clinical trials are ongoing [60,61]. Stratified medicine involves the use of diagnostic tests to reveal specific disease mechanisms (endotypes) enabling linked, mechanistically-targeted therapy [21,31]. On the other hand, untargeted (empirical) treatment may contribute to avoidable episodes of care, frustration, and adverse cardiovascular events.

6.2. Individualised care plan

Patients with a new and established diagnosis of ANOCA/INOCA can benefit from having a personal care plan. This can be developed by the patient, clinician, and allied health professionals. The care plan should include cardiac rehabilitation and a timeline for medical review. Since patients with ANOCA/INOCA may report intolerance to exertion, a tailored rehabilitation plan is recommended. A program of cardiac rehabilitation for a patient with a recent diagnosis of ANOCA/INOCA can provide integrated care for management of cardiovascular risk factors, lifestyle measures and assessments of the response to therapy, in coordination with medical care [1,2,30,43]. The plan can serve as an actionable guide for different clinical scenarios, including co-morbid health problems, self-management, and thresholds for escalating care. The care plan should take account of the lived experience, including impact on home life, partner relationship, work, and social life (including disability benefits, if appropriate), sex life, mental health, and outlook [29]. More research is needed to clarify the optimal forms of care plans.

The initial medical contact should involve an in-person meeting in the clinic and the doctor-patient relationship will be key to achieve relief of symptoms through the titration of medical therapy. Follow-up assessments may be undertaken using online tools e.g., Microsoft® Teams, or by telephone. However, if a patient has persisting symptoms that may require changes in medication, then an in-person clinical review is recommended to measure heart rate, blood pressure, and body weight and to perform a clinical examination, and obtain relevant diagnostic tests, including a non-invasive stress test (i.e. exercise ECG or functional imaging) and a coronary CTA, as clinically appropriate. Looking forward, advances in medical technologies, such as smartphone-based ECG self-monitoring of treatment responses, may be helpful to clarify myocardial ischaemia in the community [55,62]. This highlights why clinical standards for ANOCA/INOCA (Table 1) merit updates on emerging clinical evidence.

Treatment of multisystem conditions is considered in the Supplement.

6.3. Pharmacological therapy of angina

Given the lack of appropriately powered, randomized trial evidence, medical therapy in ANOCA/INOCA is based upon "expert opinion" and pathophysiological considerations [1,2,65]. Prevention based on lifestyle optimization and risk factor control (hypertension, diabetes and dyslipidaemias) [1,2,66,67] is of paramount importance considering the guarded prognosis of this population [55–58]. The WARRIOR trial is comparing an intensive medical care strategy using low dose aspirin, a high potency statin and a maximally tolerated RAS blocker versus usual care [60].

Angina therapy should be based on pathophysiological

considerations. In patients with microvascular or epicardial spasm the therapy of choice is represented by vasodilators including nitrates, calcium-antagonists and nicorandil [68, 69]. In patients with impaired cardiovascular dilation resulting in a reduction of CFR, drugs which reduce or optimize myocardial oxygen consumption are indicated as is also the case in patients in whom the reduction of CFR is caused by coronary atherosclerosis. These drugs include beta-blockers, ivabradine, ranolazine and trimetazidine [1]. Symptoms that respond to sublingual nitroglycerin indicate oral nitrate therapy may be helpful [1].

Following the initial prescription, the response to treatment should be assessed within a timeline determined by the patient and healthcare professional. The interval should account for the burden of angina (including frequency and severity), patient preference, and feasibility. For example, a patient experiencing angina once per month could merit quarterly review and a patient experiencing more burdensome angina should be reviewed earlier. A follow-up contact could be in-person or involve telephone or video consultation. A healthcare professional in primary and/or secondary care should contact the patient to assess the response to treatment. Patients with persisting symptoms should preferably be reviewed in-person rather than online, however a telehealth approach may be necessary for patients living in remote areas. The 'whole patient' should be considered including the occurrence of any side-effects (if any), anginal symptoms, co-morbidity, adherence to therapy, the need for alteration of the dose (increase or decrease) and/or dosing interval, and the prescription of second-line medication for angina. Dose escalation (if tolerated) represents an important therapeutic step in improving patient's symptoms, especially in vasospastic angina patients. The angiotensin converting enzyme inhibitor quinapril, in large doses, led to patient benefits (reduced SAQ angina and improved coronary flow reserve) in a National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE) sub-study [70]. Stratified medicine based on CFR has also been assessed in a phenotype-blinded, open-label clinical trial of medical therapy [71].

Patients with refractory angina may benefit from specialist advice involving a case-based review with peer professionals. Novel approaches, such as co-prescription of a dihydropyridine calcium channel blocker with either diltiazem or verapamil, are evidence-based and may be helpful [68]. However, amlodipine plasma concentrations are increased by diltiazem and enhanced blood pressure monitoring may be necessary. Ankle oedema may occur necessitating checks with appropriate dose adjustment or, if appropriate, use of a diuretic. Such an approach should involve a cardiologist with specialist experience in ANOCA/INOCA.

Currently, device-based [NCT04606459, NCT05492110, NCT04892537] and cell-based management [72] of ANOCA/INOCA is undergoing clinical evaluation. The role of other management strategies such as the use of heat, pacing, meditation, and mindfulness warrants further consideration.

7. Managed clinical networks

7.1. General principles

A clinical service for ANOCA/INOCA should "consider the whole patient" and provide a multidisciplinary, patient-centred service This model of healthcare can be achieved through implementation of a managed clinical network (Supplement).

7.2. Patient forums and patient partnership groups

Forums are popular and widely used by patients with lived experience of ANOCA/INOCA. These forums enable knowledge exchange on various aspects of ANOCA/INOCA, highlight case studies, disease self-management, regional variations in services, facilitate discussion on clinical practice, including gaps and horizon scanning, and serve as a portal for presentations by subject matter experts. Patient forums also provide an opportunity for the provision of emotional support and an understanding of the complexities involved in seeking diagnosis and treatment.

INOCA International [41] is a patient led initiative where patients work in partnership with clinicians, healthcare professionals, researchers, and other organizations, to improve awareness and to bring about a clearer understanding of INOCA conditions around the world. The International Heart Spasms Alliance (IHSA) is a global initiative founded by experts by experience, working in a collaborative equal partnership with clinicians, researchers, healthcare professionals and other organizations [42]. These organizations and other groups provide support for patients, raising awareness, championing research, and engaging with external stakeholders.

8. Clinical research

Participation in clinical research can improve the overall standard of clinical care and give access to the latest medical tests and treatments. Accordingly, there should be provision for research in ANOCA/INOCA services and patients should also be given the opportunity to participate in research studies wherever possible.

8.1. Challenges and limitations

In resource-constrained healthcare systems, where staff are limited, providing a standardized multidisciplinary care model may prove challenging. Outpatient waiting times may become prolonged. Telemedicine may be helpful, but challenging to implement in low resource centres.

8.2. Future developments

This document lays the framework for future rounds of clinical standards development, potentially involving a consensus-based, Delphi approach [73], with the aim of optimizing patient care and reducing unwanted variation. The clinical management and care pathways for acute myocardial infarction with no obstructive coronary arteries (MINOCA) are distinct from INOCA. Clinical standards for MINOCA would also seem to be relevant for future development.

CRediT authorship contribution statement

Colin Berry: Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Paolo G. Camici:** Writing – review & editing. **Filippo Crea:** Writing – review & editing. **Maria George:** Writing – review & editing. **Juan Carlos Kaski:** Writing – review & editing. **Peter Ong:** Writing – review & editing. **Carl J. Pepine:** Writing – review & editing. **Annette Pompa:** Writing – review & editing. **Udo Sechtem:** Writing – review & editing. **Hiroaki Shimokawa:** Writing – review & editing. **Christopher Zeitz:** Writing – review & editing. **Javier Escaned:** Writing – review & editing. **Tim P. van de Hoef:** Writing – review & editing. **John F. Beltrame:** Writing – review & editing. **C. Noel Bairey Merz:** Writing – review & editing.

Declaration of competing interest

Colin Berry is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AskBio, AstraZeneca, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, HeartFlow, Menarini, Novartis, Siemens Healthcare, Zoll Medical and Valo Health.

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Appendix A. Supplementary data

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