EuroIntervention
2025;21:e293-e295
published online e-edition March 2025
DOI: 10.4244/EIJ-E-24-00072

Routine diagnosis of ANOCA/INOCA: pros and cons

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Increasing awareness of angina or ischaemia with non-obstructive coronary arteries (ANOCA/INOCA) has expanded our knowledge of ischaemic heart disease, highlighting the importance of vasomotor disorders and microvascular dysfunction in symptomatic patients without stenoses in epicardial coronary arteries. ANOCA/INOCA encompasses a wide spectrum of conditions which require advanced diagnostic tools for precise endotyping. Emerging evidence suggests that the use of invasive functional assessments can help to identify specific mechanisms underlying myocardial ischaemia, leading to a more accurate diagnosis that enables specific treatments and – eventually – prognostic benefits. However, it should be noted that the evidence supporting routine functional assessments is limited, with guidelines recommending more selective approaches, due to considerations of procedural risks, high costs, and the lack of robust outcome data. Whether invasive functional diagnosis of ANOCA/INOCA should be adopted as a standard practice remains an area of uncertainty.

Pros

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A sizeable proportion (up to 50%) of patients undergoing coronary angiography due to suspected angina and/or detectable ischaemia have non-obstructed coronary arteries. In these patients, the role of coronary vasomotor disorders has been more frequently recognised and consequently investigated in recent years[1].

Diagnostic testing for ANOCA/INOCA may be performed using non-invasive techniques such as positron emission tomography (PET), adenosine-stress cardiac magnetic resonance imaging or stress echocardiography coupled with an anatomical coronary imaging exam such as computed tomographic coronary angiography (CTCA) to rule out obstructive coronary artery disease (CAD). However, only a comprehensive invasive functional assessment in the catheterisation laboratory permits a precise definition of the ANOCA/INOCA endotype. This diagnostic work-up includes the evaluation of adenosine-derived indices (fractional flow reserve, coronary flow reserve [CFR] and index of microvascular resistance [IMR]) along with intracoronary acetylcholine (ACh) provocation testing to detect the occurrence of epicardial or microvascular spasm. This strategy allows us to identify four ANOCA/INOCA endotypes: (1) microvascular angina, characterised by the evidence of coronary microvascular dysfunction (CMD), defined as CFR <2.0, IMR ≥25, or microvascular spasm; (2) vasospastic angina, defined by epicardial spasm in the absence of CMD (CFR ≥2.0, IMR <25); (3) a mixed type, which involves the coexistence of CMD and epicardial spasm; and (4) non-cardiac chest pain in case of normal microvascular and epicardial coronary function[1].

The advantages of routine invasive assessment with endotype characterisation in ANOCA/INOCA are multiple.

Diagnosis. Invasive functional assessment allows the ruling out or confirmation of the ischaemic origin of the patient's symptoms. This is particularly important in light of recent clinical guidelines recommending CTCA as a first-line diagnostic technique for suspected anginal chest pain and low or moderate likelihood of obstructive CAD[2], possibly resulting in an increased proportion of patients referred for invasive coronary angiography without prior functional stress testing, thus without information on ischaemia at the time of the invasive procedure.

Treatment. ANOCA/INOCA patients represent a heterogeneous population, and a comprehensive diagnostic work-up empowers cardiologists to initiate personalised therapy based on the specific mechanism underlying the myocardial ischaemia.

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The CorMicA (Coronary Microvascular Angina) trial demonstrated that stratified medicine with endotype-specific therapies, guided by invasive functional assessment results, yielded improved outcome in terms of quality of life compared to standard care[3]. One might argue that a pragmatic approach may be to routinely administer a trial of medical therapy in all symptomatic patients and assess their response over time. However, without comprehending the pathophysiology of myocardial ischaemia, the choice of the optimal medical therapy may often be a coin toss, and, in some cases, can exacerbate symptoms (e.g., in patients with epicardial spasm, beta blockers are contraindicated as they may enhance vasoconstrictive responses, whereas calcium channel blockers should represent the first-line therapy). Notably, in the CorMicA trial, more than half of treating clinicians changed their initial diagnosis and treatment following disclosure of the invasive functional assessment results[3].

Prognosis. An impaired CFR (<2.5) has been unequivocally associated with an increased rate of major adverse cardiac events (MACE) over a 5 year follow-up period in ANOCA/INOCA patients[4]. Furthermore, intracoronary ACh provocation testing has been shown to be a safe procedure, able to identify patients with a worse prognosis in terms of MACE and quality of life both in myocardial infarction and non-obstructive coronary arteries (MINOCA)[5] and in ANOCA/INOCA[6], especially in case of epicardial spasm.

Patient's perspective. Providing a definite diagnosis can empower patients, encouraging them to adopt preventive lifestyle measures and adhere to treatment, thereby enhancing treatment satisfaction and engagement.

In conclusion, ANOCA/INOCA frequently remains undiagnosed and untreated, resulting in persistent symptoms and increased risk of cardiovascular events. Routine assessment is essential for achieving an early diagnosis and initiating timely, tailored management, ultimately improving patient outcomes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Cons

Annapoorna Kini, MD; Keisuke Yasumura, MD

The evolving understanding of ANOCA/INOCA has led to shifts in clinical practice, particularly in diagnostic approaches. Invasive diagnostic testing now includes assessments for coronary microvascular dysfunction, vasospasm, and myocardial bridging, thereby expanding the diagnostic landscape. Here, we discuss the limitations of adopting routine diagnosis of ANOCA/INOCA.

The first limitation concerns the lack of consensus and evidence. The 2024 ESC Guidelines for the management of chronic coronary syndromes emphasise the importance of identifying ANOCA/INOCA and provide a structured framework for doing so[2]. However, they recommend a targeted, rather than routine diagnostic approach. Current ACC/AHA guidelines for management of chest pain lack substantial updates on ANOCA/INOCA[7], reflecting ongoing uncertainty. This lack of consensus points to the need for further evidence to clarify the role of routine testing in these conditions.

Other limitations involve resources, cost, and risk. Routine diagnostic testing with invasive functional assessments (e.g., CFR, IMR, and ACh testing) and advanced non-invasive imaging modalities (e.g., PET, stress CMR imaging) are both costly and resource-intensive for health care systems, placing financial and procedural burdens on patients. Supporting routine testing for all patients with potential ANOCA/INOCA presents challenges, with inconsistent reimbursement policies for advanced diagnostics, which increase financial barriers. Under these constraints, allocating resources toward established cardiovascular tests with proven benefits may be more cost-effective than widespread testing for ANOCA/INOCA, especially considering patient-specific variability in functional testing outcomes and the lack of definitive outcome data for these conditions[8].

These diagnostic tests also carry inherent risks. Vasospasm assessment requires provocative testing with acetylcholine or ergonovine, which can induce arrhythmias such as atrioventricular block (requiring temporary pacing) and ventricular fibrillation due to left main coronary artery spasm[9]. Evaluation of myocardial bridging involves intravascular imaging and functional testing under intravenous dobutamine stress with a flow wire, which adds both cost and risk. While these procedures are essential for targeted treatment, thorough informed consent is necessary to ensure patients understand the associated risks. Additionally, to avoid inaccurate or incomplete results, patients should discontinue caffeine and certain medications, such as beta blockers or calcium channel blockers, before functional testing. Without these preparations, routine coronary functional testing may yield suboptimal assessments.

The final limitation relates to patient management. Epicardial coronary artery disease through invasive or non-invasive coronary angiography is a critical initial step in managing chest pain, as it addresses potentially life-threatening cardiovascular risks and alleviates patient anxiety. Rather than implementing routine testing for ANOCA/INOCA in all patients, a symptom-based selective approach may be more pragmatic, particularly for those with persistent or severe symptoms. This strategy allows diagnostic resources to focus on those most likely to benefit, while patients with mild or intermittent symptoms can avoid unnecessary invasive procedures. For patients with ongoing, unexplained symptoms, further testing can be considered, as its impact on long-term outcomes remains uncertain[10].

The management of ANOCA/INOCA does not align with the guideline-directed medical therapy for obstructive coronary artery disease, and optimal treatment strategies for ANOCA/INOCA remain elusive. This is largely due to the heterogeneity of underlying mechanisms, the potential

overlap of multiple conditions, and the lack of robust randomised trials evaluating specific therapeutic pathways. Thus, selective and conservative management aligns with a precision medicine approach, aiming to tailor interventions based on symptom severity and individual patient needs.

In conclusion, considering the lack of consensus, concerns about cost-effectiveness, and limited treatment data, routine diagnosis of ANOCA/INOCA may not be justified. While advancements in diagnostic testing provide valuable insights, a personalised, symptom-based approach may be more appropriate for optimising patient care.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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