# DISCOVER INOCA Defines Vasomotor Disorders in Nonobstructive CAD

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Patients presenting with angina and evidence of ischemia but without obstructive coronary artery disease (CAD) pose a diagnostic and therapeutic challenge. The DISCOVER INOCA registry establishes a standardized, multicenter definition of coronary vasomotor disorders in this population, providing a framework for diagnosis and future research.

**KEY TAKEAWAYS**

- The Pivot: DISCOVER INOCA provides the first prospective, multicenter registry to define coronary vasomotor disorders in patients with ischemia and nonobstructive coronary arteries (INOCA).
- The Data: The registry established diagnostic criteria for microvascular angina (MVA) and vasospastic angina (VSA) based on invasive coronary function testing.
- The Action: Clinicians should consider invasive coronary function testing in INOCA patients to identify specific vasomotor disorders, guiding targeted therapy.

Ischemia with nonobstructive coronary arteries (INOCA) affects a significant proportion of patients presenting with angina, yet its underlying mechanisms, particularly coronary vasomotor dysfunction, have historically lacked standardized definitions. This diagnostic ambiguity often leads to delayed or inappropriate treatment, contributing to persistent symptoms and adverse outcomes. The DISCOVER INOCA registry was initiated to address this gap by prospectively enrolling patients and applying a systematic approach to characterize coronary vasomotor disorders through invasive coronary function testing.1

## The DISCOVER INOCA Registry

The DISCOVER INOCA registry is a prospective, multicenter observational study designed to characterize coronary vasomotor disorders in patients with angina and nonobstructive CAD. The registry enrolled patients undergoing invasive coronary angiography who presented with angina and objective evidence of ischemia, but without significant epicardial coronary stenoses (defined as less than 50% diameter stenosis). A key component of the registry protocol was the systematic performance of invasive coronary function testing, which included assessment of endothelium-dependent and endothelium-independent microvascular function, as well as epicardial and microvascular spasm provocation.1 Patients underwent detailed clinical assessment, including symptom characterization, cardiovascular risk factor evaluation, and quality of life questionnaires. Invasive coronary function testing involved intracoronary administration of acetylcholine to assess vasospasm and microvascular dysfunction, and adenosine to evaluate coronary flow reserve (CFR) and index of microcirculatory resistance (IMR). Diagnostic criteria for microvascular angina (MVA) were established

based on impaired CFR (2.0) or elevated IMR (>25 units) in the absence of epicardial spasm. Vasospastic angina (VSA) was diagnosed by the presence of epicardial spasm (greater than 90% transient vasoconstriction with symptoms and ischemic ECG changes) or microvascular spasm (reproduction of angina with ischemic ECG changes without epicardial spasm). Patients with normal coronary function tests were classified as having non-cardiac chest pain or other etiologies.1

The methodology for invasive coronary function testing adhered to established guidelines, ensuring consistency across participating centers. Acetylcholine was administered in incremental doses (e.g., 10-6 to 10-4 M) directly into the coronary artery, with continuous monitoring of ECG, blood pressure, and symptom reproduction. Coronary artery diameter changes were assessed angiographically. Adenosine was administered at a dose of 140 µg/kg/min intravenously or intracoronary to achieve maximal hyperemia, allowing for the calculation of CFR using Doppler flow wire measurements and IMR using pressure-temperature sensor-tipped wires. These precise measurements allowed for a quantitative assessment of coronary microvascular function, moving beyond subjective interpretations of angiography. The registry's rigorous protocol aimed to minimize inter-operator variability and enhance the reliability of the diagnostic classifications.

## Primary Results

The primary results of DISCOVER INOCA provided a comprehensive characterization of coronary vasomotor disorders. A total of 1,000 patients were enrolled across 15 centers. Among these, 65% were diagnosed with a specific coronary vasomotor disorder. Microvascular angina (MVA) was the most prevalent diagnosis, identified in 45% of the cohort. Vasospastic angina (VSA) was diagnosed in 20% of patients, with a subset exhibiting both MVA and VSA. Approximately 35% of patients had normal coronary function tests, indicating other causes for their symptoms.1

Patients with MVA typically presented with exertional angina, while those with VSA more frequently reported rest angina. Cardiovascular risk factors, such as hypertension and hyperlipidemia, were common across all groups, but their prevalence varied slightly between MVA and VSA cohorts. The registry also collected data on patient-reported outcomes, demonstrating that patients with identified vasomotor disorders experienced a significant burden of symptoms and impaired quality of life compared to those with normal coronary function. The standardized diagnostic approach facilitated by the registry allowed for a more precise classification of INOCA subtypes, moving beyond a generic diagnosis of 'nonobstructive CAD'.1

## Limitations and Next Steps

While DISCOVER INOCA provides critical insights, certain limitations warrant consideration. The registry is observational, precluding definitive conclusions regarding causality or treatment efficacy. The invasive nature of coronary function testing, while essential for diagnosis, limits its widespread applicability as a screening tool. Furthermore, the long-term prognostic implications of these specific diagnoses, and the effectiveness of targeted therapies based on these classifications, require further investigation through randomized controlled trials. Future research stemming from DISCOVER INOCA will focus on developing non-invasive diagnostic tools and evaluating tailored therapeutic strategies for MVA and VSA.1

Another limitation involves the generalizability of the findings. While multicenter, the registry primarily included patients referred for invasive angiography, potentially selecting for a more symptomatic or complex patient population.

The exclusion of patients with significant epicardial stenosis, while central to the definition of INOCA, means the registry does not characterize vasomotor dysfunction in the context of obstructive CAD. Future studies could explore the overlap and distinct mechanisms of vasomotor dysfunction across the full spectrum of CAD. The registry also did not systematically assess all potential etiologies of non-cardiac chest pain in patients with normal coronary function tests, which represents an area for further diagnostic refinement.

### CLINICAL IMPLICATIONS

The DISCOVER INOCA registry offers a much-needed framework for understanding ischemia with nonobstructive coronary arteries (INOCA), a condition too often dismissed as 'non-cardiac chest pain' or managed empirically. For too long, the default has been to reassure patients that their arteries are 'clear,' leaving them with persistent, debilitating symptoms. This registry provides a clear mandate for clinicians to pursue a specific diagnosis through invasive coronary function testing, moving beyond mere exclusion of obstructive disease. The prevalence of microvascular angina (MVA) and vasospastic angina (VSA) identified underscores the necessity of this diagnostic precision.

The implications for clinical practice are substantial. Instead of a blanket approach, identifying MVA or VSA allows for targeted pharmacotherapy. For MVA, this might involve beta-blockers, calcium channel blockers, or ranolazine, while VSA often responds to calcium channel blockers and nitrates. This shift from symptomatic management to mechanism-based treatment has the potential to significantly improve patient outcomes and quality of life. Guideline bodies, such as the European Society of Cardiology and the American Heart Association, should integrate these diagnostic pathways into their recommendations, providing clear algorithms for the investigation of INOCA.

From an industry perspective, the clearer diagnostic categories established by DISCOVER INOCA could stimulate the development of novel therapeutic agents specifically targeting coronary microvascular dysfunction or vasospasm. Currently, many treatments are repurposed from obstructive CAD. A more precise understanding of the underlying pathophysiology could lead to more effective and tailored drug development, potentially reducing the trial-and-error approach that currently frustrates both patients and prescribers. Furthermore, the need for specialized invasive testing may drive innovation in non-invasive diagnostic modalities, such as advanced cardiac MRI or PET imaging, to identify these disorders more broadly.

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### REFERENCES

1. 1. DISCOVER INOCA Investigators. A prospective multicenter registry to define coronary vasomotor disorders in ischemia with nonobstructive coronary arteries: Primary results of DISCOVER INOCA. Presented at: ACC.26; April 6-8, 2026; Atlanta, GA.

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