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Review Article

Ischemia with No Obstructive Coronary Arteries (INOCA): Diagnostic Approaches and Contemporary Treatment Strategies

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Abstract

Ischemia with No Obstructive Coronary Arteries (INOCA) is increasingly recognized as a distinct clinical syndrome characterized by objective evidence of myocardial ischemia in the absence of flow-limiting epicardial coronary artery disease. Once considered a benign finding, INOCA is now known to be associated with persistent symptoms, impaired quality of life, recurrent hospitalizations, and adverse cardiovascular outcomes. The condition is highly prevalent among patients undergoing coronary angiography for angina, with a pronounced predominance in women, underscoring important sex specific pathophysiological mechanisms. INOCA encompasses heterogeneous underlying mechanisms, most notably coronary microvascular dysfunction and epicardial coronary vasospasm, which may occur in isolation or coexist. These abnormalities result in dynamic and context dependent ischemia that is frequently missed by conventional diagnostic pathways focused on obstructive coronary disease. As a result, INOCA remains underdiagnosed and undertreated in routine clinical practice. This review provides a comprehensive and contemporary overview of INOCA, integrating current knowledge on its pathophysiology, clinical presentation, diagnostic strategies, and management approaches. We highlight the limitations of traditional anatomy based evaluation and emphasize the importance of functional and mechanism-oriented diagnostic frameworks, including advanced non-invasive imaging and invasive coronary function testing. Particular attention is given to phenotype-guided therapeutic strategies, encompassing targeted anti-ischemic therapy, endothelial and disease modifying treatments, and lifestyle and non-pharmacological interventions. By synthesizing emerging evidence and clinical insights, this review advocates for a multidisciplinary, personalized approach to INOCA. Adoption of mechanism based diagnostic and therapeutic strategies has the potential to improve symptom control, optimize long-term outcomes, and align INOCA management with the principles of modern, patient centered cardiovascular care.

Keywords: carcinoid tumor; pulmonary neoplasm; multiple foci

Introduction

Ischemia with No Obstructive Coronary Arteries (INOCA) describes a clinical syndrome in which patients experience objective evidence of myocardial ischemia despite the absence of significant obstructive epicardial coronary artery disease on coronary angiography. Traditionally, the detection of non-obstructive coronary arteries has often led to reassurance and symptom attribution to non cardiac causes. However, growing evidence challenges this assumption and highlights INOCA as a distinct and clinically relevant cardiovascular entity associated with persistent symptoms, impaired quality of life, and adverse outcomes [1,2].

The terminology surrounding ischemic syndromes without obstructive coronary disease has evolved and can be confusing in clinical practice. INOCA refers specifically to chronic ischemic symptoms or signs in the absence of flow limiting coronary stenoses. ANOCA (Angina with No Obstructive Coronary Arteries) is a symptom based term that emphasizes anginal chest pain without demonstrable ischemia, whereas MINOCA (Myocardial Infarction with No Obstructive Coronary Arteries) describes an acute coronary syndrome phenotype with myocardial injury. Although these entities overlap, INOCA occupies a unique position as a chronic ischemic condition with heterogeneous mechanisms and often elusive diagnostic findings [3,4].

Epidemiologically, INOCA is common. Among patients undergoing coronary angiography for stable angina or suspected ischemic heart disease, a substantial proportion are found to have non-obstructive coronary arteries.

This phenomenon is particularly prominent in women, who represent the majority of INOCA cases across multiple clinical settings. Sex specific differences in coronary pathophysiology, hormonal influences, and microvascular function likely contribute to this distribution, underscoring the need for tailored diagnostic and therapeutic approaches [5,6].

A central paradox of INOCA lies in the dissociation between angiographic findings and clinical risk. The absence of obstructive coronary artery disease does not equate to a benign prognosis. Patients frequently experience recurrent angina, repeated hospital admissions, and ongoing functional limitation. Moreover, ischemia in INOCA reflects genuine myocardial supply demand mismatch, often driven by abnormalities at the microvascular or vasomotor level rather than fixed epicardial stenosis [7,8].

Despite its prevalence and clinical impact, INOCA remains underdiagnosed and undertreated. Diagnostic challenges arise from heterogeneous underlying mechanisms, including coronary microvascular dysfunction, epicardial coronary vasospasm, or a combination of both. Conventional diagnostic algorithms centered on obstructive coronary disease frequently fail to identify these abnormalities. Therapeutic uncertainty further compounds the problem, as standardized management strategies are lacking and treatment is often empirical rather than mechanism based [9,10].

The aim of this review is to provide a comprehensive overview of INOCA, integrating current understanding of its pathophysiology, clinical presentation, diagnostic approaches, and contemporary treatment strategies. By emphasizing a structured, mechanism-oriented framework, this review seeks to bridge existing gaps in recognition and management and to support a more personalized approach to patients with ischemia and non-obstructive coronary arteries.

Pathophysiological Mechanisms of INOCA

INOCA is not a single disease entity but rather a clinical syndrome arising from diverse pathophysiological mechanisms that impair myocardial perfusion in the absence of obstructive epicardial coronary artery disease. This heterogeneity explains the wide spectrum of clinical presentations, variable responses to therapy, and frequent diagnostic uncertainty observed in daily practice. Among these mechanisms, coronary microvascular dysfunction (CMD) represents the most prevalent and extensively studied substrate of INOCA (11). The heterogeneous mechanisms underlying INOCA, including coronary microvascular dysfunction, epicardial coronary vasospasm, and mixed phenotypes, along with their typical triggers and diagnostic clues, are summarized in Table 1.

CMD reflects an inability of the coronary microcirculation to appropriately augment blood flow in response to increased myocardial oxygen demand. Because the coronary microvasculature cannot be directly visualized by conventional angiography, functional abnormalities often remain undetected unless specific physiological assessments are performed. Importantly, CMD may occur in isolation or coexist with epicardial vasomotor disorders, further contributing to dynamic and context-dependent ischemia [12].

Mechanism	Key Pathophysiology	Typical Triggers	Diagnostic Clues	Clinical Phenotype
Coronary Microvascular Dysfunction (CMD)	Impaired microvascular vasodilation, increased microvascular resistance, reduced coronary flow reserve	Physical exertion, tachycardia, mental stress	Reduced CFR on PET/CMR/invasive testing, normal epicardial arteries	Effort-related angina, exercise intolerance
Epicardial Coronary Vasospasm	Transient focal or diffuse coronary artery spasm due to smooth muscle hyperreactivity	Rest, nocturnal episodes, emotional stress, cold exposure	Ischemic ECG changes during pain, positive acetylcholine test	Rest angina, circadian variation
Mixed CMD and Vasospasm	Coexistence of microvascular dysfunction and epicardial spasm	Both exertional and rest-related triggers	Combined abnormalities on invasive testing	Variable symptoms, refractory angina
Systemic and Contributing Factors	Endothelial dysfunction, autonomic imbalance, inflammation, hormonal influences	Psychosocial stress, metabolic derangements	No single diagnostic marker; supportive clinical context	Fluctuating, context-dependent ischemia

Table 1: Pathophysiological Mechanisms of INOCA.

Abbreviations: INOCA: Ischemia with No Obstructive Coronary Arteries, CMD: Coronary Microvascular Dysfunction, CFR: Coronary Flow Reserve, PET: Positron Emission Tomography, CMR: Cardiac Magnetic Resonance, ECG: Electrocardiography

Coronary Microvascular Dysfunction (CMD)

CMD is broadly categorized into structural and functional endotypes. Structural CMD is characterized by anatomical alterations of the microcirculation, including arteriolar wall thickening, capillary rarefaction, and increased microvascular resistance. These changes are frequently associated with chronic cardiovascular risk factors such as hypertension, diabetes mellitus**,** and left ventricular hypertrophy, leading to persistently reduced coronary flow reserve (CFR) [13].

In contrast, functional CMD primarily reflects abnormal vasomotor regulation without fixed structural remodeling. This phenotype is driven by impaired endothelium dependent and endothelium independent vasodilation, resulting in an inadequate increase in myocardial blood flow during stress. Endothelial nitric oxide bioavailability plays a central role, and its dysfunction contributes to abnormal microvascular tone and heightened ischemic susceptibility [11].

Microvascular remodeling represents a final common pathway in many patients with CMD, linking functional abnormalities to irreversible structural changes over time. Progressive impairment of CFR has been consistently associated with worse clinical outcomes, reinforcing the concept that CMD is not a benign finding but a clinically meaningful determinant of ischemia and prognosis in INOCA [12,13].

Epicardial Coronary Vasospasm

Epicardial coronary vasospasm represents a dynamic and reversible cause of myocardial ischemia in patients with INOCA and is characterized by transient, excessive vasoconstriction of the epicardial coronary arteries. Vasospasm may present as focal spasm, typically localized to a single coronary segment and often associated with atherosclerotic plaques, or as diffuse spasm, which involves long segments of the coronary tree and reflects a more generalized vasomotor disorder (14). These phenotypes have distinct clinical and prognostic implications and may coexist with microvascular dysfunction.

Endothelial dysfunction plays a central role in the pathogenesis of epicardial vasospasm. Impaired bioavailability of nitric oxide leads to a loss of normal vasodilatory responses and a paradoxical vasoconstrictive reaction to stimuli such as acetylcholine. This abnormal endothelial signaling predisposes coronary arteries to hyperreactivity and episodic ischemia, even in angiographically normal vessels [15].

Beyond endothelial nitric oxide dysfunction, activation of the Rho-kinase pathway has emerged as a key molecular mechanism underlying coronary vasospasm. Rho-kinase enhances calcium sensitivity in vascular smooth muscle cells, promoting sustained vasoconstriction independent of intracellular calcium levels. Increased Rho-kinase activity has been demonstrated in patients with vasospastic angina and correlates with disease severity, providing both mechanistic insight and a potential therapeutic target [16]. Collectively, these mechanisms underscore the active and regulated nature of epicardial vasospasm in INOCA rather than a purely functional or incidental phenomenon.

Combined Pathophysiological Mechanisms

In clinical practice, INOCA frequently reflects the coexistence of coronary microvascular dysfunction (CMD) and epicardial coronary vasospasm, rather than a single isolated abnormality. Invasive coronary function testing studies have demonstrated that a substantial proportion of patients exhibit overlapping microvascular impairment and abnormal epicardial vasoreactivity, highlighting the multidimensional nature of ischemia in this population [11,14].

This overlap gives rise to dynamic and context-dependent ischemia, where myocardial perfusion varies according to physiological stress, autonomic tone, circadian influences, or pharmacologic triggers. CMD may dominate during exercise-related ischemia due to impaired coronary flow reserve, whereas vasospastic mechanisms often manifest at rest or during emotional stress, leading to transient but profound reductions in coronary blood flow [12,15]. Such variability explains fluctuating symptoms, inconsistent non-invasive test results, and the frequent mismatch between angiographic findings and clinical burden.

Recognizing combined pathophysiological mechanisms is critical, as integrated diagnostic strategies have been shown to improve symptom control and guide more effective, personalized treatment in INOCA [17].

Systemic and Contributing Factors

Beyond coronary specific abnormalities, systemic factors play a critical modulatory role in the development and expression of ischemia in INOCA. Dysregulation of the autonomic nervous system is increasingly recognized as a contributor, particularly through heightened sympathetic activity and impaired parasympathetic tone. Autonomic imbalance can promote coronary vasoconstriction, amplify microvascular resistance, and precipitate ischemia under physical or emotional stress [12,15].

Inflammation and oxidative stress further exacerbate microvascular and endothelial dysfunction. Chronic low grade inflammation impairs nitric oxide bioavailability, promotes vascular smooth muscle hyperreactivity, and accelerates microvascular remodeling, thereby lowering the ischemic threshold even in the absence of fixed coronary obstruction [11,18].

Hormonal influences, especially fluctuations in estrogen levels, are thought to partially explain the female predominance of INOCA. Estrogen deficiency has been linked to endothelial dysfunction, altered autonomic regulation, and increased vasomotor instability, particularly in postmenopausal women [18].

Finally, metabolic syndrome and insulin resistance contribute to CMD through endothelial dysfunction, inflammation, and impaired microvascular vasodilation. These systemic conditions reinforce the concept of INOCA as a multisystem disorder rather than an isolated coronary phenomenon [13,19].

Clinical Presentation and Risk Profile

Patients with INOCA present with a wide spectrum of symptoms that often differ from those observed in classic obstructive coronary artery disease, contributing to frequent misdiagnosis and delayed recognition. Although typical exertional angina may occur, many patients report atypical chest pain characteristics, including prolonged discomfort, variable intensity, or pain that is poorly responsive to nitrates [19,20]. These features challenge traditional ischemic paradigms that emphasize fixed epicardial stenosis as the primary driver of symptoms.

A hallmark of INOCA is the high prevalence of non–exertional chest pain, frequently occurring at rest or triggered by emotional stress rather than physical activity. Such patterns are particularly common in patients with vasomotor dysfunction and may reflect dynamic changes in coronary tone or autonomic imbalance rather than demand-driven ischemia [17,20]. As a result, standard exercise-based diagnostic algorithms may underestimate disease burden.

Beyond chest pain, dyspnea, fatigue, and exercise intolerance are frequent presenting complaints. These symptoms often dominate the clinical picture and may be disproportionate to findings on coronary angiography or conventional stress testing. Impaired coronary microvascular reserve, abnormal ventricular vascular coupling, and heightened sympathetic activation have all been implicated in limiting functional capacity in INOCA [12,21].

The cardiovascular risk profile of patients with INOCA overlaps substantially with that of obstructive coronary disease. Hypertension, diabetes mellitus, obesity, and smoking are highly prevalent and contribute to endothelial dysfunction and microvascular remodeling [11,13]. Importantly, psychosocial stress plays a prominent role, particularly in women, and has been linked to symptom severity, recurrent healthcare utilization, and reduced quality of life [20,22].

These diverse manifestations give rise to recognizable clinical phenotypes and symptom clusters, including predominantly exertional ischemia, rest-related vasospastic symptoms, and mixed patterns with fluctuating triggers. Appreciating this heterogeneity is essential, as symptom burden and risk cannot be inferred solely from angiographic findings. Instead, INOCA requires a patient-centered assessment that integrates symptom patterns, systemic risk factors, and underlying pathophysiological mechanisms.

Diagnostic Approaches in INOCA

Initial Clinical Evaluation

The diagnostic evaluation of patients with suspected INOCA begins with a comprehensive clinical assessment, as symptom characteristics and baseline risk profile provide critical clues to underlying pathophysiology. A detailed symptom history should extend beyond the presence or absence of exertional chest pain and explore temporal patterns, triggers, duration, response to

nitrates, and associations with emotional stress or rest. Such features are particularly important in identifying vasomotor or microvascular ischemia, which often presents with atypical or fluctuating symptom profiles [20,23].

Estimation of pre-test probability of coronary artery disease remains an essential step, although traditional models largely focus on obstructive epicardial disease. In patients with INOCA, pre-test probability tools should be interpreted cautiously, as a low likelihood of obstructive CAD does not exclude clinically relevant ischemia. Contemporary frameworks emphasize integrating age, sex, symptom quality, and cardiovascular risk factors to guide downstream testing while avoiding premature diagnostic closure following a "normal" coronary angiogram [23,24].

Resting electrocardiography (ECG) is routinely performed but is often normal or nonspecific in INOCA. Nonetheless, baseline ECG may reveal repolarization abnormalities, prior silent infarction, or conduction disturbances that influence diagnostic strategy and risk stratification. Importantly, the absence of ischemic changes at rest should not deter further evaluation when symptoms are suggestive [24].

Transthoracic echocardiography (TTE) plays a central role in the initial assessment. While left ventricular systolic function is typically preserved, echocardiography allows exclusion of alternative causes of symptoms such as valvular disease, cardiomyopathies, or pericardial pathology. Subtle findings, including impaired diastolic function, increased left ventricular mass, or abnormal ventricular–vascular coupling, may support a diagnosis of microvascular ischemia and provide prognostic information [21,25]. In selected patients, advanced echocardiographic parameters such as global longitudinal strain may further refine risk assessment.

Overall, meticulous initial clinical evaluation establishes the foundation for targeted diagnostic testing and helps identify patients in whom ischemia persists despite non-obstructive coronary arteries.

Non-Invasive Functional Testing

Non-invasive functional testing is a cornerstone in the evaluation of suspected INOCA, yet each modality has inherent strengths and limitations that must be recognized to avoid false reassurance. Exercise treadmill testing (ETT) remains widely used but has limited sensitivity and specificity in INOCA. Ischemia in this population is often dynamic, non–flow-limiting, or stress-context dependent, leading to frequent false-negative results, particularly in women and patients with microvascular dysfunction [23,26].

Stress echocardiography improves diagnostic yield by assessing inducible wall motion abnormalities and hemodynamic responses. However, because microvascular ischemia may not produce regional contractile abnormalities, stress echocardiography can underestimate ischemic burden in INOCA. Ancillary findings such as abnormal blood pressure response, reduced exercise capacity, or diastolic dysfunction may provide indirect evidence of ischemia despite preserved systolic function [24,27].

Myocardial perfusion imaging plays a central role in detecting functional ischemia. SPECT is widely available and useful for identifying regional perfusion defects, but its spatial resolution and susceptibility to attenuation artifacts limit its ability to detect diffuse microvascular ischemia. As a result, balanced or global reductions in perfusion may be missed [26].

In contrast, PET imaging allows absolute quantification of myocardial blood flow and coronary flow reserve (CFR), making it particularly valuable in INOCA. Reduced CFR on PET provides robust evidence of coronary microvascular dysfunction and carries important prognostic implications, even in the absence of obstructive coronary disease [21,28].

Cardiac magnetic resonance imaging (CMR) has emerged as a powerful modality in INOCA assessment. Stress perfusion CMR offers high spatial resolution and enables detection of subendocardial ischemia typical of microvascular disease. In addition, tissue characterization with late gadolinium enhancement and parametric mapping allows identification of myocardial fibrosis, inflammation, or alternative diagnoses, thereby refining both diagnosis and risk stratification [29].

Overall, optimal non invasive evaluation in INOCA requires thoughtful selection of imaging modalities, with preference for techniques capable of assessing microvascular function rather than relying solely on inducible regional ischemia.

Invasive Coronary Assessment

In patients with persistent symptoms despite non-invasive testing, invasive coronary assessment plays a pivotal role in uncovering the underlying mechanisms of INOCA. Conventional coronary angiography remains essential to exclude flow limiting epicardial stenosis; however, its diagnostic yield is limited when used in isolation. Angiographically "normal" or mildly diseased vessels do not preclude functionally significant ischemia, particularly when abnormalities reside at the microvascular or vasomotor level [23,30]. Invasive physiological assessment enables direct interrogation of coronary function beyond luminal anatomy. Measurement of coronary flow reserve (CFR) provides an integrated index of epicardial and microvascular function, while the index of microcirculatory resistance (IMR) specifically quantifies microvascular resistance independent of hemodynamic conditions. Reduced CFR and/or elevated IMR are hallmark findings of coronary microvascular dysfunction and have been consistently associated with adverse clinical outcomes [30,31].

In contrast, fractional flow reserve (FFR) has a limited role in INOCA. While invaluable for assessing intermediate epicardial stenoses, FFR may be normal in patients with diffuse atherosclerosis or microvascular disease, potentially leading to false reassurance if interpreted without complementary indices [31].Coronary vasoreactivity testing with intracoronary acetylcholine or ergonovine is the gold standard for diagnosing epicardial and microvascular vasospasm. This approach allows differentiation between focal or diffuse epicardial spasm and microvascular spasm based on angiographic response, ischemic symptoms, and electrocardiographic changes. Importantly, vasoreactivity testing is safe when performed in experienced centers and provides actionable diagnostic information that directly guides therapy [14,16,17].

Overall, invasive coronary assessment represents a transformative step in the evaluation of INOCA, shifting the diagnostic paradigm from anatomical exclusion to mechanism-based diagnosis and enabling personalized management strategies.

Diagnostic Algorithms

Given the heterogeneity of INOCA, structured diagnostic algorithms are essential to avoid underdiagnosis and fragmented care. Contemporary guideline based diagnostic pathways emphasize a transition from an anatomy-centered approach toward a function- and mechanism-oriented evaluation. After exclusion of obstructive coronary artery disease, patients with persistent symptoms should undergo targeted functional assessment rather than being reassured based solely on angiographic findings [23,24].

A stepwise evaluation strategy is recommended. Initial clinical assessment and non invasive functional testing help identify patients with objective ischemia or high symptom burden. When non-invasive tests are inconclusive or discordant with symptoms, invasive coronary function testing including assessment of coronary flow reserve, microvascular resistance, and vasoreactivity provides definitive mechanistic classification. This approach enables differentiation between microvascular angina, vasospastic angina,

mixed phenotypes, and non-cardiac chest pain, thereby guiding personalized therapy (17,22).

Importantly, the feasibility of these algorithms in real world clinical practice has been demonstrated. While comprehensive invasive testing is not universally available, simplified pathways that integrate symptom profiling, selective advanced imaging, and referral to experienced centers can substantially improve diagnostic accuracy and clinical outcomes. Adoption of standardized diagnostic algorithms represents a critical step toward closing the gap between guideline recommendations and everyday management of patients with INOCA (32,23). A phenotype-based diagnostic and therapeutic framework integrating non-invasive and invasive coronary function testing is outlined in Table 2.

Dominant Phenotype	Key Diagnostic Findings	Preferred Diagnostic Tests	First-Line Therapy	Drugs to Avoid
CMD predominant	Reduced CFR, elevated IMR, absence of epicardial spasm	PET with CFR, stress CMR, invasive CFR/IMR	Beta-blockers, ACEi/ARB, statins, ranolazine	Long-acting nitrates (limited efficacy)
Vasospastic Angina	Epicardial spasm with ischemic symptoms and ECG changes	Coronary angiography with acetylcholine testing	High-dose CCBs, long-acting nitrates	Non-selective beta-blockers, triptans
Mixed Phenotype	Both CMD and vasospasm present	Comprehensive invasive coronary function testing	Combination therapy (CCB + beta-blocker or ranolazine)	Phenotype-inappropriate monotherapy
Unclear / Indeterminate	Persistent symptoms, inconclusive tests	Stepwise escalation, referral to expert centers	Symptom-guided therapy + risk factor control	-

Table 2: Phenotype-Based Diagnostic and Therapeutic Strategies in INOCA.

Abbreviations: INOCA: Ischemia with No Obstructive Coronary Arteries, CMD: Coronary Microvascular Dysfunction, CFR: Coronary Flow Reserve, IMR: Index of Microcirculatory Resistance, PET: Positron Emission Tomography, CMR: Cardiac Magnetic Resonance, ECG: Electrocardiography, ACEi: Angiotensin-Converting Enzyme Inhibitors, ARB: Angiotensin Receptor Blockers, CCBs: Calcium Channel Blockers

Prognosis and Clinical Outcomes

INOCA has long been perceived as a benign condition due to the absence of obstructive coronary artery disease; however, accumulating evidence clearly refutes this misconception. Patients with INOCA experience a substantial burden of major adverse cardiovascular events (MACE), recurrent symptoms, and impaired long-term outcomes that rival or, in selected subgroups, approach those observed in obstructive coronary disease [33].

Large observational cohorts have demonstrated that patients with angina and non-obstructive coronary arteries are at increased risk of recurrent hospitalizations driven by persistent chest pain, repeated diagnostic testing, and ongoing therapeutic uncertainty. These recurrent healthcare encounters reflect not only symptom burden but also delayed recognition of the underlying ischemic mechanisms [20,33].

The impact on quality of life is profound. Patients with INOCA frequently report limitations in physical activity, reduced exercise tolerance, and significant psychosocial distress. Importantly, quality-of-life impairment is often disproportionate to angiographic findings and may persist despite reassurance following a “normal” coronary angiogram, highlighting the inadequacy of anatomy based risk assessment alone [19,20].

From a prognostic perspective, long term outcomes are strongly influenced by the underlying endotype. Impaired coronary flow reserve (CFR), a hallmark of coronary microvascular dysfunction, has been consistently associated with increased risk of cardiovascular death and heart failure hospitalization, independent of epicardial disease severity [18,24]. In contrast, patients with predominantly vasospastic phenotypes often experience recurrent ischemic episodes and arrhythmic events but may exhibit more favorable survival when appropriately diagnosed and treated [14,16,35].

These prognostic differences underscore the importance of mechanism based diagnosis in INOCA. Recognition of CMD identifies a subgroup with diffuse vascular disease and higher long term risk, whereas vasospastic angina represents a dynamic but potentially reversible condition when targeted therapy is instituted. Collectively, these data establish INOCA as a clinically meaningful syndrome requiring active risk stratification and longitudinal management rather than diagnostic dismissal. Beyond symptom burden, INOCA is associated with recurrent hospitalizations, major adverse cardiovascular events, and an increased risk of HFpEF, underscoring its prognostic relevance (Figure 1).

Contemporary Treatment Strategies in INOCA

General Treatment Principles

Effective management of INOCA relies on a phenotype guided therapeutic strategy, reflecting the heterogeneity of its underlying mechanisms. Rather than applying uniform antianginal therapy, treatment should be tailored according to the dominant endotype coronary microvascular dysfunction, epicardial vasospasm, or mixed phenotypes identified through functional assessment

[17,36]. This mechanism based approach represents a fundamental shift from anatomy driven care toward precision cardiovascular medicine.

The primary therapeutic objectives are symptom relief and prognostic improvement. Symptom control is critical, as patients with INOCA frequently experience persistent angina, reduced functional capacity, and impaired quality of life despite the absence of obstructive coronary disease. Standard reassurance following a “normal” angiogram is insufficient and may contribute to ongoing morbidity and repeated healthcare utilization [19,20].

Beyond symptomatic benefit, targeted therapy may influence disease trajectory by improving endothelial function, reducing microvascular resistance, and stabilizing coronary vasomotor tone. In particular, recognition of microvascular angina as a distinct clinical entity has facilitated more rational treatment selection and avoidance of ineffective therapies [36]. Concurrently, comprehensive cardiovascular risk factor management including control of blood pressure, glycemic status, lipid levels, and psychosocial stress is essential and should be implemented across all INOCA phenotypes.

Overall, general treatment principles in INOCA emphasize individualized, mechanism oriented care with dual goals of alleviating ischemic symptoms and addressing long term cardiovascular risk.

Anti-Ischemic Pharmacological Therapy

Pharmacological treatment in INOCA should be individualized according to the dominant ischemic mechanism, as drug efficacy varies substantially across phenotypes. Beta blockers are commonly used in patients with coronary microvascular dysfunction, particularly when symptoms are exertional. By reducing heart rate, myocardial oxygen demand, and diastolic filling time mismatch, beta blockers may improve ischemic tolerance in CMD. However, they should be used cautiously in patients with suspected vasospastic angina, where unopposed alpha adrenergic activity may exacerbate spasm [37,38]. Mechanism-specific pharmacological options, their preferred clinical phenotypes, expected benefits, and key limitations are summarized in Table 3.

Drug Class	Target Mechanism	Best-Suited Phenotype	Expected Benefit	Limitations / Cautions
Beta blockers	Reduced heart rate and myocardial oxygen demand	CMD-predominant	Improved exertional angina, exercise tolerance	May worsen vasospasm
CCBs	Coronary smooth muscle relaxation	Vasospastic and mixed phenotypes	Prevention of coronary spasm, symptom relief	Hypotension, bradycardia (non-DHP)
Nitrates	Vasodilation of large coronary vessels	Vasospastic angina	Relief of rest angina	Limited benefit in CMD, tolerance
Ranolazine	Improved myocardial relaxation via late Na^+ current inhibition	CMD predominant, refractory angina	Reduced angina frequency, improved QoL	QT prolongation, drug interactions
Ivabradine	Selective heart rate reduction	CMD with elevated resting HR	Improved diastolic perfusion time	Limited data, bradycardia
ACEi / ARBs	Endothelial function improvement	CMD, metabolic comorbidities	Improved CFR, prognostic benefit	Hypotension, renal monitoring
Statins	Anti-inflammatory and endothelial effects	All phenotypes	Improved microvascular function, risk reduction	Myopathy, liver enzyme elevation

Table 3: Pharmacological Therapies in INOCA According to Mechanism

Abbreviations: INOCA: Ischemia with No Obstructive Coronary Arteries, CMD: Coronary Microvascular Dysfunction, CCBs: Calcium Channel Blockers, DHP: Dihydropyridine, Na^+: Sodium ion, QoL: Quality of Life, HR: Heart Rate, ACEi: Angiotensin-Converting Enzyme Inhibitors, ARBs: Angiotensin Receptor Blockers, CFR: Coronary Flow Reserve.

Calcium channel blockers (CCBs) represent first-line therapy for epicardial coronary vasospasm. Both dihydropyridine and non-dihydropyridine agents effectively reduce vasomotor tone and prevent spontaneous or provoked coronary spasm. CCBs may also provide symptomatic benefit in microvascular angina by improving microvascular vasodilation, making them particularly useful in mixed phenotypes [14,16,38].

Nitrates, while effective in obstructive coronary disease, have important limitations in INOCA. Many patients with microvascular angina report minimal or inconsistent symptom relief, likely due to preferential dilation of larger vessels without meaningful impact on the microcirculation. Long-acting nitrates may be beneficial in vasospastic angina but should be avoided or used cautiously in pure CMD [37].

Ranolazine has emerged as a valuable option for patients with persistent symptoms despite conventional therapy. By inhibiting late sodium current and improving myocardial relaxation, ranolazine may reduce ischemia related to microvascular dysfunction without significant hemodynamic effects. Clinical studies suggest modest but meaningful improvements in angina frequency and quality of life in selected INOCA populations [39].

Ivabradine, through selective heart rate reduction, may improve symptoms in patients with CMD by optimizing diastolic perfusion time. Its role is adjunctive and best suited for patients with elevated resting heart rate who remain symptomatic despite beta blocker or CCB therapy [40].

Endothelial and Disease-Modifying Therapies

In INOCA, endothelial dysfunction represents a central pathophysiological mechanism linking ischemic symptoms to adverse long-term outcomes. Consequently, disease-modifying therapies aimed at improving endothelial function are essential components of management, particularly in patients with coronary microvascular dysfunction.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) improve endothelial function through multiple mechanisms, including reduction of oxidative stress, attenuation of vascular inflammation, and reversal of microvascular remodeling. Clinical studies in patients with non-obstructive coronary disease have demonstrated improvements in coronary flow reserve and anginal symptoms, supporting their use beyond blood pressure control alone, especially in patients with CMD or metabolic comorbidities [41].

Statins exert pleiotropic vascular effects independent of lipid lowering. By enhancing nitric oxide bioavailability, reducing inflammatory signaling, and stabilizing vascular smooth muscle tone, statins contribute to improved microvascular function. Evidence suggests that statin therapy is associated with improved endothelial-dependent vasodilation and reduced ischemic burden in patients with angina and non-obstructive coronary arteries, reinforcing their role as foundational therapy in INOCA [42].

Finally, anti-inflammatory approaches are increasingly recognized as relevant in INOCA, given the contribution of chronic low-grade inflammation to endothelial dysfunction and microvascular disease. Although large randomized trials specifically targeting inflammation in INOCA are lacking, mechanistic and observational data support inflammation as a modifiable therapeutic target and an important area for future investigation [43].

Management of Vasospastic Angina

The cornerstone of treatment for vasospastic angina is high-dose calcium channel blockers (CCBs), which effectively suppress coronary smooth muscle hyperreactivity and prevent spontaneous or provoked spasm. Both dihydropyridine and non-dihydropyridine CCBs are effective, and combination therapy may be required in refractory cases [38,44].

Long-acting nitrates serve as adjunctive therapy by promoting vasodilation and reducing vasospastic episodes, particularly in patients with nocturnal or rest angina. However, tolerance may develop with chronic use, and nitrates should not replace CCBs as first-line therapy [44,45].

Importantly, several drugs should be avoided in vasospastic angina. Non-selective beta blockers may worsen coronary spasm by unopposed alpha adrenergic activity, and triptans or ergot derivatives can provoke severe vasoconstriction. Recognition of the vasospastic phenotype is therefore essential to prevent iatrogenic exacerbation of ischemia and arrhythmic risk [45].

Lifestyle and Non-Pharmacological Interventions

Lifestyle modification and non-pharmacological strategies play a complementary yet essential role in the management of INOCA. Structured exercise programs improve endothelial function, enhance coronary flow reserve, and reduce symptom burden, particularly in patients with coronary microvascular dysfunction. When delivered within a cardiac rehabilitation framework, exercise training is associated with improved functional capacity, quality of life, and symptom perception, even in the absence of obstructive disease [46].

Given the strong interaction between ischemic symptoms and autonomic tone, stress reduction strategies are particularly relevant. Psychological stress can precipitate ischemia through sympathetic activation and vasomotor instability. Accordingly, psychological interventions, including cognitive behavioral therapy and stress management programs, have demonstrated benefits in symptom control and health-related quality of life, especially in women with INOCA [20,47].

Tailored Therapy Based on Coronary Function Testing

Tailored therapy guided by coronary function testing represents a major advance in the management of INOCA. Stratified treatment strategies that incorporate invasive assessment of coronary flow reserve, microvascular resistance, and vasoreactivity allow precise identification of the dominant ischemic mechanism and selection of targeted therapy. Evidence from randomized studies demonstrates that mechanism-based treatment leads to significant improvements in angina severity, quality of life, and patient satisfaction compared with standard care [17].

The clinical impact of personalized management extends beyond symptom control. By avoiding ineffective therapies and directing treatment toward the underlying pathophysiology, tailored approaches reduce diagnostic uncertainty and recurrent healthcare utilization. These data support the integration of coronary function testing into contemporary care pathways for selected patients with persistent symptoms and suspected INOCA [17].

Special Populations and Emerging Concepts

INOCA disproportionately affects women, who represent the majority of patients presenting with angina and non-obstructive coronary arteries. Sex specific differences in endothelial function, coronary microvascular regulation, hormonal influences, and autonomic balance contribute to this predominance. Women with INOCA frequently experience higher symptom burden, atypical presentations, and greater impairment in quality of life, often leading to delayed diagnosis and under-recognition [20].

An important emerging concept is the association between INOCA and heart failure with preserved ejection fraction (HFpEF). Coronary microvascular dysfunction is increasingly viewed as a shared pathophysiological substrate linking myocardial ischemia to diastolic dysfunction, increased ventricular stiffness, and exercise intolerance. Reduced coronary flow reserve has been shown to predict incident HFpEF and adverse outcomes, suggesting that INOCA and HFpEF may reflect different clinical expressions of systemic microvascular disease [25,48].

The autonomic nervous system plays a key role in modulating coronary vasomotor tone and myocardial perfusion. Heightened sympathetic activation and impaired parasympathetic reserve can precipitate ischemia in the absence of epicardial obstruction, particularly during emotional stress. This mechanism provides a biological link between psychosocial stressors and ischemic symptoms in INOCA [47,49].

Accordingly, mental stress induced ischemia has gained increasing attention, especially in women. Mental stress can provoke ischemia through microvascular constriction, endothelial dysfunction, and inflammatory activation, even when conventional exercise stress testing is normal [47,49].

Finally, emerging biomarkers and novel therapeutic targets are under active investigation. Circulating markers of inflammation, endothelial dysfunction, and microvascular injury, along with advanced imaging-derived phenotypes, may enable earlier diagnosis, refined risk stratification, and more personalized treatment strategies in INOCA [48,50].

Future Directions and Research Gaps

Despite growing recognition of INOCA as a clinically meaningful syndrome, substantial gaps remain in its diagnosis and management. A central unmet need is the standardization of diagnostic criteria across non-invasive and invasive modalities. Variability in definitions of coronary microvascular dysfunction, thresholds for coronary flow reserve, and criteria for vasospastic responses hampers comparability across studies and limits implementation of guideline-recommended pathways in routine practice [42].

Another major limitation is the lack of large, randomized therapeutic trials powered for hard clinical endpoints. Most available evidence derives from small mechanistic studies or observational cohorts, leaving uncertainty regarding the long term prognostic impact of specific pharmacological strategies. This gap underscores the need for multicenter trials evaluating phenotype guided therapy on cardiovascular outcomes rather than symptom relief alone (17,32).

Digital health and remote monitoring represent promising tools to address the fluctuating and context dependent nature of ischemia in INOCA. Wearable sensors, mobile symptom tracking, and home based physiological monitoring may enable real time correlation between symptoms, autonomic tone, and ischemic burden, potentially improving longitudinal management and patient engagement [51]. Advances in artificial intelligence (AI) are poised to transform imaging interpretation and patient phenotyping. AI driven analysis of CMR, PET, and echocardiographic data may uncover subtle microvascular patterns and integrate multimodal datasets to refine diagnosis beyond human pattern recognition [52].

Ultimately, these developments converge toward precision medicine approaches in INOCA. By integrating clinical features, coronary function testing, imaging biomarkers, and digital phenotypes, future care models may deliver individualized risk stratification and targeted therapy, moving beyond anatomy-based paradigms toward truly personalized cardiovascular care [53].

Conclusions

Ischemia with No Obstructive Coronary Arteries represents a distinct and clinically significant cardiovascular syndrome that challenges traditional, anatomy-centered concepts of ischemic heart disease. Accumulating evidence demonstrates that the absence of flow limiting epicardial stenosis does not imply a benign condition. Instead, INOCA encompasses heterogeneous mechanisms, most commonly coronary microvascular dysfunction and epicardial vasospasm, which give rise to persistent ischemic symptoms, impaired quality of life, and increased long-term cardiovascular risk.This review highlights the importance of moving beyond conventional diagnostic pathways that rely solely on coronary angiography. Comprehensive evaluation integrating careful clinical assessment, advanced non-invasive imaging, and selective invasive coronary function testing enables identification of the dominant ischemic mechanism and supports more accurate diagnosis. Such an approach addresses a major source of diagnostic uncertainty and helps avoid inappropriate reassurance or ineffective treatment.

From a therapeutic perspective, management of INOCA should be individualized and mechanism based. Phenotype-guided pharmacological therapy, combined with aggressive cardiovascular risk factor modification and non-pharmacological interventions, offers the greatest potential for symptom relief and meaningful improvement in patient outcomes. Importantly, recognition of INOCA as a chronic condition underscores the need for longitudinal care rather than episodic symptom management.

In daily clinical practice, effective care for patients with INOCA requires a multidisciplinary approach involving cardiologists, imaging specialists, rehabilitation teams, and, when appropriate, behavioral health professionals. Embracing a mechanism based framework not only improves diagnostic accuracy and therapeutic precision but also aligns INOCA management with the principles of contemporary, patient centered cardiovascular medicine.

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