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Beyond the blockage: A review of myocardial infarction with non-obstructive coronary arteries

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Abstract

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a syndrome in which patients have clear signs of heart muscle injury but show <50% stenosis on coronary angiography. We recognize it as a distinct condition that demands its own diagnostic and treatment approaches. Recent studies were reviewed to elucidate the pathophysiology, diagnostic criteria, and management strategies for MINOCA. PubMed, Scopus, and Google Scholar were searched for full-text, peer-reviewed articles on MINOCA's pathophysiology and diagnostics. Keywords such as "non-obstructive coronary artery," "ischemic heart diseases," and "myocardial infarction" were used. Following the screening and synthesis of the selected papers, we found that MINOCA can result from ischemic causes—plaque disruption, vasospasm, microvascular dysfunction, spontaneous coronary artery dissection, and coronary embolism—as well as from non-ischemic causes, such as myocarditis and Takotsubo cardiomyopathy. The diagnostic evaluation of MINOCA relies on high-sensitivity troponin assays, coronary angiography, cardiac magnetic resonance (CMR) imaging, optical coherence tomography, and functional testing for vasomotor disorders. There are emerging biomarkers, including microRNAs, copeptin, and soluble suppression of tumorigenicity-2, that help refine the risk assessment. We concluded that MINOCA requires a stepwise diagnostic algorithm and personalized treatment methods tailored to the underlying cause, while advocating for early use of CMR imaging, targeted imaging or functional tests, and long-term follow-up. Future randomized trials are warranted to validate etiology-specific therapies and imaging-guided management strategies.

Keywords: Myocardial infarction; Non-obstructive coronary artery disease; Biomarkers; Heart muscle injury; Coronary vasospasm

1. Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a unique form of acute coronary syndrome (ACS). It does not show significant blockages in the coronary arteries, unlike the classical type of myocardial infarction (MI). Instead, patients show signs of heart muscle injury without major coronary obstruction. MINOCA has many causes, including coronary vasospasm, microvascular dysfunction, plaque disruption, and non-ischemic conditions, such as myocarditis and Takotsubo cardiomyopathy.[1] These diverse causes make both diagnosis and treatment challenging. Advances in imaging and laboratory tests have deepened our understanding of this condition. This review gathers recent literature on the pathophysiology and diagnostic methods of MINOCA. Our goal is to provide clear insights that help clinicians connect the patient's initial presentation with a definitive diagnosis.

2. Literature search and screening methods

This narrative review was conducted by carefully searching the literature to identify studies that explored the underlying mechanisms and diagnostic approaches specific to MINOCA. We primarily searched the PubMed, Scopus, and Google Scholar databases using keywords such as "non-obstructive coronary artery," "ischemic heart diseases," and "myocardial infarction." This strategy ensured that we captured relevant research articles, with a focus on the most recent advancements in the field.

The inclusion criteria were full-text, peer-reviewed articles or review papers that primarily addressed the pathophysiology or diagnostic methods for MINOCA. The articles that did not meet these specifications were excluded. The chosen articles were then meticulously reviewed. We synthesized these findings to produce a detailed narrative that highlights the evolving concepts in diagnosing and understanding MINOCA.

3. Pathophysiology

The pathophysiology of MINOCA is a complex interplay of multiple factors and needs further research. Unlike the classical presentation of obstructive coronary artery disease as a cause of MI, MINOCA presents with similar signs and symptoms, but its coronary angiography shows no obstructive stenosis (usually defined as <50% luminal narrowing).[2,3] This contradiction can be attributed to a variety of underlying mechanisms, including ischemic and non-ischemic factors, that can cause actual myocardial injury. Ischemic causes include plaque disruption, coronary vasospasm, and microvascular dysfunction, whereas non-ischemic causes are myocarditis and Takotsubo cardiomyopathy.[2-4] The underlying mechanisms can be identified using modalities such as cardiac magnetic resonance (CMR) imaging, optical coherence tomography (OCT), and coronary functional testing (Table 1).[3,4]

3.1. Epicardial mechanism (plaque disruption and thrombosis)

The most common ischemic mechanism in MINOCA is plaque disruption, including rupture, erosion, and calcified nodules with thrombus. Plaque disruption is observed in approximately 24–35% of MINOCA patients, particularly those with subclinical atherosclerotic changes that may not be evident on coronary angiography.[5,6] Research on OCT revealed that plaque disruption is frequently accompanied by intracoronary thrombus and closely linked to ischemic findings on CMR imaging (Magnetic resonance imaging [MRI]).[6] In addition, female sex is more often associated with layered plaque or intraplaque hemorrhage, pointing to a sex-related variation in plaque morphology.[7]

3.2. Coronary vasospasm

Coronary vasospasm is defined as a reversible >90% constriction of the epicardial and microvascular coronary vessels, resulting in ischemia.[8] It is primarily attributed to decreased nitric oxide bioavailability due to endothelial dysfunction, inflammatory processes, and oxidative stress, which collectively induce vascular spasm.[9] Another mechanism involves vascular smooth muscle hyperreactivity mediated through the activation of Rho-kinase (ROCK), which can be reversed by fasudil.[10]

3.3. Coronary microvascular dysfunction (CMD)

CMD involves both structural (e.g., arteriolar fibrosis) and functional (e.g., endothelial dysfunction and microvascular spasm) causes. It is one of the major mechanisms of MINOCA and may occur with or without vasospasm.[10]

3.4. Spontaneous coronary artery dissection (SCAD)

SCAD involves the presence of an intramural hemorrhage due to an intimal tear, which ultimately reduces the size of the true lumen by creating a false lumen.[11,12] SCAD most commonly occurs in young women and is often associated with fibromuscular dysplasia as well as pregnancy-related or hormonal changes.[12]

3.5. Coronary embolism and *in situ* thrombosis

Approximately 3% of MINOCA cases are caused by coronary emboli (due to atrial fibrillation or prosthetic valves) and *in situ* thrombosis (due to hypercoagulable states or plaque disruption).[13] According to studies, about 24% of MINOCA patients demonstrate inherited thrombophilia (such as Factor V Leiden and antiphospholipid syndrome).[14]

Table 1. Pathophysiological mechanisms of MINOCA

Category	Mechanism	Key features	Prevalence
Ischemic	Plaque disruption and thrombosis	Rupture/erosion on OCT, intracoronary thrombus, MRI ischemia[5,6]	24–35% of MINOCA cases[5,6]
	Coronary vasospasm	>90% reversible stenosis, endothelial dysfunction, Rho-kinase[8-10]	Variable (up to 20%) [8,9]
	Microvascular dysfunction	Arteriolar fibrosis, endothelial dysfunction, microspasm[10]	Common in women[10]
	Spontaneous coronary artery dissection	Intramural hemorrhage, false lumen, fibromuscular dysplasia[11,12]	5–15%, young females[12]
	Coronary embolism and *in situ* thrombosis	Emboli (AF and valves), hypercoagulable states, inherited thrombophilia[13,14]	~3%[13]
Non-ischemic	Myocarditis	Viral or autoimmune inflammation, mid-wall LGE on CMR imaging[15]	31–33% of MINOCA cases[15]
	Takotsubo cardiomyopathy	Stress trigger, apical ballooning, no LGE on CMR imaging[15]	10–18%[15]
	Other cardiomyopathies	Dilated/hypertrophic patterns, variable LGE[15]	12–15%[15]

Abbreviations: AF: Atrial fibrillation; CMR: Cardiac magnetic resonance; LGE: Late gadolinium enhancement; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MRI: Magnetic resonance imaging; OCT: Optical coherence tomography.

3.6. Non-ischemic causes

The non-ischemic causes of MINOCA include:

- Myocarditis: In a meta-analysis study, it was revealed that myocarditis is the most common non-ischemic cause of MINOCA (31–33% of patients)[15]
- Takotsubo (stress) cardiomyopathy: This represents 10–18% of MINOCA patients according to CMR studies[15]
- Other non-ischemic cardiomyopathies: Another 12–15% of cases include dilated and hypertrophic cardiomyopathies (Table 1).

3.7. Advanced pathophysiological insights in MINOCA

Sex-specific mechanisms exist in MINOCA. There is a higher prevalence of CMD and SCAD in females. In MINOCA, 35% of cases in women <50 years are due to SCAD. On the other hand, CMD is induced by estrogen deficiency and small vessel size.[16] Estrogen exerts a protective effect by increasing endothelial nitric oxide synthase activity, leading to nitric oxide production and vasodilation. Hence, when the estrogen level falls following menopause, a person is more susceptible to CMD and vasospasm.[17] In addition, factors such as gestational diabetes, hypertension in pregnancy, and systemic inflammation are known to increase the risk of CMD in females with MINOCA.[16]

Vasospasm and CMD frequently coexist, sharing overlapping mechanisms. Both conditions are largely driven by endothelial dysfunction and increased vascular smooth muscle tone mediated by ROCK activation.[18]

Several key molecular pathways are implicated in these processes. The nitric oxide/endothelial nitric oxide synthase pathway, which is activated by estrogen, promotes vasodilation. Loss or impairment of this pathway may ultimately result in CMD and spasm. Meanwhile, the ROCK pathway is another critical regulator of vascular tone; it is stimulated by inflammatory factors such as interleukin (IL)-1β and inhibited by fasudil. In addition, inflammatory markers (e.g., IL-1β), angiotensin II, and oxidative stress enhance ROCK signaling and cause endothelial injury in both microvascular and epicardial vessels.

4. Diagnosis of MINOCA

Currently, MINOCA remains a diagnostic challenge, as patients fulfill the criteria of the Fourth Universal Definition of MI but exhibit <50% stenosis on coronary angiography.[19] Unlike obstructive MI, MINOCA represents a provisional diagnostic entity that requires further evaluation to exclude alternative causes and identify the underlying ischemic pathways[20] (Table 2).

4.1. Diagnosis of MI

As discussed earlier, MINOCA adheres to the Fourth Universal Definition of MI. Cardiac troponin measurement, especially high-sensitivity assays, is necessary for detecting myocardial injury. A diagnosis of MI is confirmed by a rise and/or fall in troponin levels, alongside supporting clinical features and electrocardiographic (ECG) findings. However, conditions such as myocarditis and Takotsubo cardiomyopathy must be ruled out, as both can present with elevated troponin levels.[2]

4.2. Coronary angiography

According to angiographic criteria, MINOCA is defined by the absence of obstructive coronary artery disease, typically characterized by <50% stenosis in all major

Table 2. Diagnostic modalities for MINOCA

Test	Timing	Main purpose	Diagnostic hallmark
High-sensitivity troponin	On presentation (+ serial)	Confirm myocardial injury	Rise/fall pattern with supporting ECG[2]
ECG	Immediate	Initial assessment	ST-segment changes (elevation/inversion);[22] lack of reciprocal depression in Takotsubo syndrome[23]
Coronary angiography (+ OCT/IVUS)	Within 24 h	Exclude obstruction, detect plaque/dissection	<50% stenosis; OCT shows plaque disruption[21]
CMR imaging	Day 2–14	Tissue characterization	Subendocardial/transmural LGE (myocardial infarction); mid-wall LGE (myocarditis); apical ballooning (Takotsubo syndrome);[24] reclassification in 68% of cases[25]
Provocative vasoreactivity test	If CMR imaging is non-diagnostic	Diagnose vasospasm	≥90% constriction with symptoms/ECG changes[22]
Guidewire-based CFR/ IMR	If CMD is suspected	Quantify microvascular function	CFR <2.0 or IMR >25[26]

Abbreviations: CFR: Coronary flow reserve; CMD: Coronary microvascular dysfunction; CMR: Cardiac magnetic resonance; ECG: Electrocardiography; IMR: Index of microcirculatory resistance; IVUS: Intravascular ultrasound; LGE: Late gadolinium enhancement; MINOCA: Myocardial infarction with non-obstructive coronary arteries; OCT: Optical coherence tomography.

epicardial vessels.[19] Intravascular imaging techniques, such as OCT and intravascular ultrasound (IVUS), may be used during angiography to identify plaque disruption, dissection, or thrombus that may not be detected on conventional angiography.[21]

4.3. Electrocardiogram

The ECG is a first-line diagnostic tool in the evaluation of MINOCA, but it lacks specificity. Approximately one-third of patients present with ST-segment elevation, which often elicits initial ST-segment elevation MI-directed care. However, this finding alone cannot distinguish MINOCA from other etiologies.[22] Takotsubo syndrome commonly presents with ST-segment elevation and T-wave inversion but typically lacks reciprocal depression, further complicating ECG-based distinctions.[23] Therefore, ECG interpretation must be supplemented with biomarkers and imaging studies.

4.4. CMR imaging

Currently, CMR imaging is considered a mainstay in MINOCA evaluation and is ideally performed within 7–14 days of presentation. It provides detailed tissue characterization that enables differentiation among key etiologies:

- MI, which reveals subendocardial or transmural late gadolinium enhancement (LGE) in a vascular distribution
- myocarditis, which demonstrates mid-wall or epicardial LGE; and
- Takotsubo syndrome, which shows regional wall motion abnormalities (typically apical ballooning) without LGE.[24]

In 2018, Ferreira *et al.*[24] provided expert recommendations for the use of CMR—including the updated Lake Louise Criteria—for identifying inflammatory vs. ischemic myocardial injury in suspected non-ischemic myocarditis. In addition, a 2023 systematic review and meta-analysis by Mileva *et al.*[25] revealed that CMR facilitated a definitive diagnosis in approximately 74% of MINOCA patients, with 68% of initial diagnoses being reclassified following CMR evaluation.

4.5. Functional testing for coronary vasomotor disorders

In patients with unobstructed coronary arteries and no structural abnormalities on CMR, it is essential to assess for epicardial spasm and CMD. Invasive provocative testing using intracoronary acetylcholine or ergonovine administration remains the gold standard for diagnosing vasospasm; this requires the presence of symptoms with ischemic ECG changes and >90% vasoconstriction.[22] CMD can be identified through guidewire-based measurements, defined by a coronary flow reserve of <2.0 or an index of microcirculatory resistance of >25.[26] These conditions are more prevalent in younger women and remain underdiagnosed due to their complexity and limited availability of procedures.[27]

4.6. Differential diagnosis

The differential diagnosis includes myocarditis, Takotsubo cardiomyopathy, pulmonary embolism, and type 2 MI:

- Myocarditis: It is often post-viral and may share similar findings on ECG and troponin levels as MI, but it additionally shows diffuse ST-segment changes and non-ischemic LGE

- Takotsubo syndrome: It often presents after emotional or physical stress, with apical ballooning noted on CMR imaging and typically no LGE[28]
- Pulmonary embolism: It is rare and should be considered in case of unexplained hypoxia, right heart strain, or atypical ECG findings.

4.7. Diagnostic algorithms and pathways

Current guidelines recommend a stepwise diagnostic approach (Figure 1):

(i) Diagnose MI using ECG and troponin levels
(ii) Perform coronary angiography to exclude obstructive disease
(iii) Conduct CMR imaging within 2 weeks
(iv) If CMR imaging is non-diagnostic, proceed with intracoronary imaging (e.g., OCT) and coronary function testing (for vasospasm or CMD) to identify the underlying etiology.[2]

4.8. Emerging biomarkers and molecular tools

Conventional biomarkers such as troponin are sensitive indicators of myocardial injury but do not reliably distinguish ischemic from non-ischemic etiologies in MINOCA. Emerging biomarkers may provide additional diagnostic and prognostic value (Table 3 and Figure 2):

i. Heart-type fatty acid–binding protein: Rapidly released within 1 h after injury and more cardiac-specific than myoglobin, it enables early detection of MI—even when troponin results are negative. In MINOCA, its early release profile may help differentiate ischemic injury from myocarditis.[29]
ii. Growth differentiation factor-15 (GDF-15): As a stress-responsive cytokine elevated in ACS, GDF-15 correlates with prognosis independently of C-reactive protein (CRP) or natriuretic peptides. This marker may be particularly useful in MINOCA, where long-term outcomes are heterogeneous.[29]
iii. MicroRNAs (e.g., miR-1, miR-133a, miR-208a/b, and miR-499a-5p): Detectable within 4 h of MI onset, these microRNAs provide earlier detection than troponin and show high sensitivity and specificity in early ACS. Their ability to differentiate ischemic necrosis from Takotsubo syndrome or myocarditis may improve diagnostic clarity in MINOCA.[29]
iv. Copeptin: Copeptin is a surrogate for vasopressin. When used with troponin, its early rise provides a >99% negative predictive value to rule out MI within 3 h of chest pain onset. In suspected MINOCA, it may help avoid unnecessary prolonged observation when ischemia is less likely.[30]
v. Inflammatory biomarkers (e.g., myeloperoxidase [MPO], matrix metalloproteinase 9 [MMP-9, CRP, IL-6): Novel markers such as MPO and MMP-9 correlate with plaque instability, infarct size, and outcomes in ACS. In MINOCA, their elevation may indicate microvascular inflammation or subtle atherosclerotic activity not evident on angiography.[31]
vi. Soluble suppression of tumorigenicity-2 (ST2): A member of the IL-1 receptor family, soluble ST2 has emerged as a novel prognostic biomarker in acute MI. Its elevation reflects myocardial stress and fibrosis and is independently associated with long-term risks of heart failure and mortality, irrespective of natriuretic peptide or troponin levels. Although ST2's role in MINOCA requires further study, its strong prognostic value in conventional MI suggests potential utility in stratifying risk in MINOCA patients with uncertain long-term outcomes.[32]

Table 3. Emerging biomarkers and molecular tools

Biomarker/Tool	Onset of elevation	Role	Notes
Heart-type fatty acid–binding protein	~1 h post-injury	Early MI detection	More specific than myoglobin[29]
Growth differentiation factor-15	Acute and chronic	Prognostic stress marker	Independent of CRP and natriuretic peptides[29]
MicroRNAs (e.g., miR-1, miR-133a, miR-208a/b, and miR-499a-5p)	1–4 h	Early MI detection; high sensitivity and specificity	Promising for very early ACS diagnosis[29]
Copeptin	0–3 h	Rule out MI (NPV >99% with troponin)	Surrogate for vasopressin[30]
Inflammatory markers (e.g., MPO, MMP-9, CRP, and IL-6)	Acute	Plaque instability and infarct-size predictor	Correlate with infarct size and outcomes in ACS[31]
Soluble ST2	Acute and follow-up	Prognostic fibrosis/stress biomarker	Potential risk stratifier in MI and MINOCA[32]
Circulating endothelial cells (CEC)/ Endothelial progenitor cells (EPC)	Acute and reparative	Markers of vascular injury and repair	CEC↑ indicates injury; EPC↓predicts adverse outcomes[33,34]

Abbreviations: ACS: Acute coronary syndrome; CRP: C-reactive protein; IL-6: Interleukin 6; MI: Myocardial infarction; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MMP-9: Matrix metalloproteinase 9; MPO: Myeloperoxidase; NPV: Negative predictive value; ST2: Suppression of tumorigenicity-2.

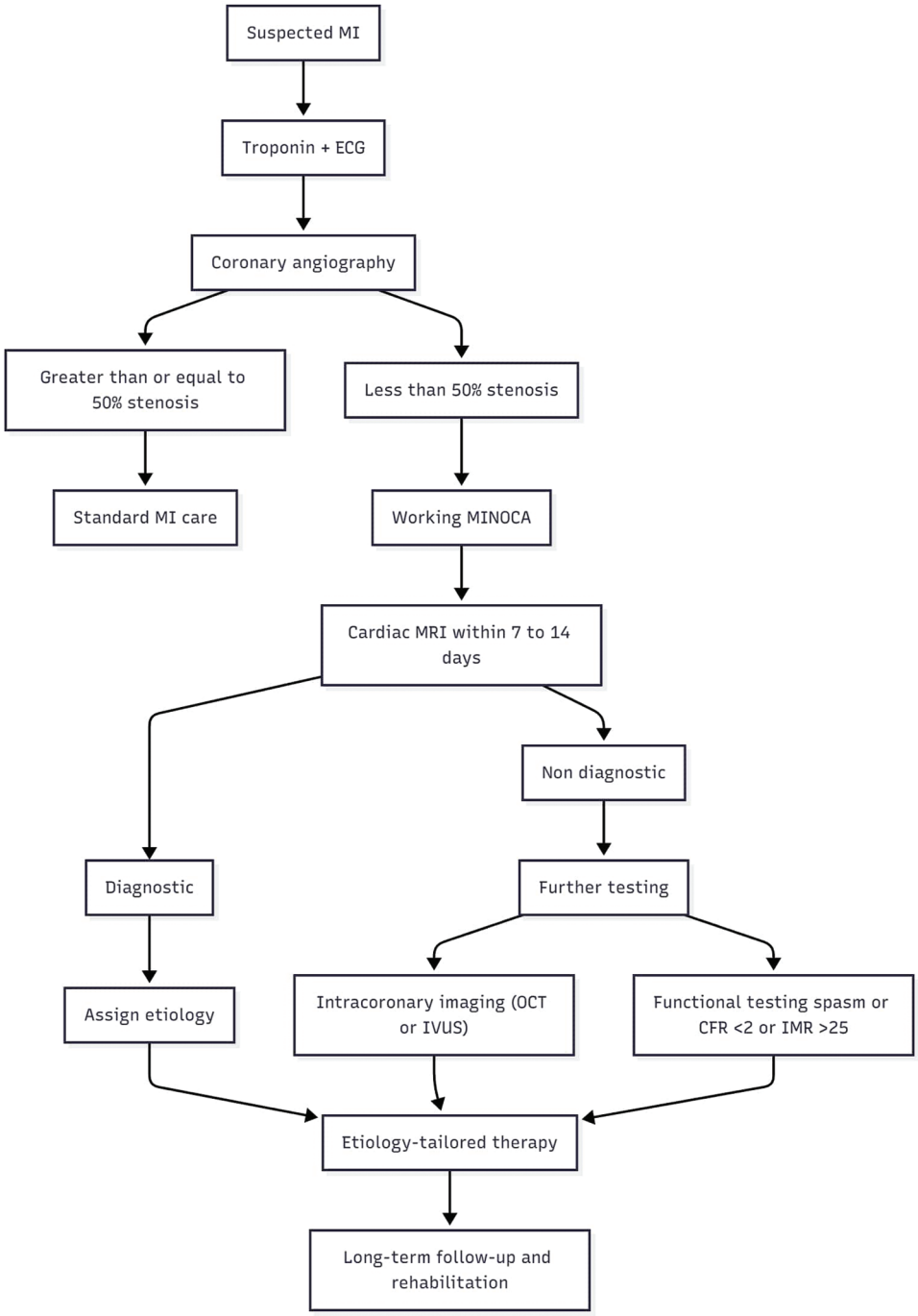

Figure 1. Stepwise diagnostic algorithm for MINOCA evaluation. Image created by the authors.
Abbreviations: CFR: Coronary flow reserve; ECG: Electrocardiography; IMR: Indfex of microcirculatory resistance; IVUS: Intravascular ultrasound; MI: Myocardial infarction; MINOCA: Myocardial infarction with non-obstructive coronary arteries; MRI: Magnetic resonance imaging; OCT: Optical coherence tomography.

vii. Endothelial/Progenitor cells: Circulating endothelial cells, markers of vascular injury, are elevated in acute MI and indicate endothelial disruption.[33] Conversely, endothelial progenitor cells, which participate in vascular repair, are inversely associated with adverse cardiovascular outcomes. In MINOCA, they may indicate microvascular inflammation or subclinical atherosclerotic activity undetectable on angiography[34] (Table 3).

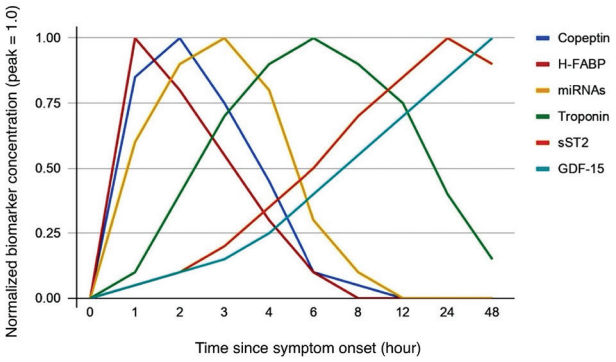

Figure 2. Temporal rise of cardiac biomarkers in MINOCA. Image created by the authors.
Abbreviations: GDF-15: Growth differentiation factor-15; H-FABP: Heart-type fatty acid–binding protein; MINOCA: Myocardial infarction with non-obstructive coronary arteries; sST2: Soluble suppression of tumorigenicity-2.

In summary, a thorough diagnostic approach that includes imaging, intracoronary assessment, and clinical context is essential to uncover the underlying etiology of MINOCA. Early use of CMR imaging, followed by targeted testing when initial investigations are inconclusive, ensures accurate classification and guides appropriate management.

5. Management

The management of MINOCA presents a unique clinical challenge due to its heterogeneous etiologies and distinct pathophysiological mechanisms. Unlike type 1 MI, MINOCA is not a single disease but rather a syndrome requiring accurate diagnostic evaluation before starting treatment. Therefore, standardized treatment protocols are not appropriate. Instead, management should be customized according to the root cause, such as plaque disruption, microvascular dysfunction, coronary spasm, myocarditis, or Takotsubo syndrome. Nevertheless, a comprehensive therapeutic approach is often used in the acute setting while the specific etiology remains unknown.[2,35]

5.1. General medical therapy

Guided by principles of limiting myocardial injury and optimizing secondary prevention, the initial treatment of MINOCA frequently resembles that of type 1 MI until a specific etiology is confirmed. However, the efficacy of this approach remains uncertain and is still a topic of ongoing investigation. Clinicians must strike a balance between early empirical treatment and the need to refine treatment based on diagnostic clarity, as highlighted in recent studies.[36,37]

5.1.1. Aspirin

Aspirin is commonly prescribed for its proven benefit in atherothrombotic episodes and favorable safety profile. Its efficacy in non-atherosclerotic conditions such as myocarditis and vasospasm, however, has not been established.[38,39]

5.1.2. Statins

Statins are recommended for the majority of MINOCA patients, especially when an atherosclerotic component is suspected, owing to their pleiotropic effects, including plaque stabilization, anti-inflammatory action, and endothelial function improvement. A 2022 meta-analysis showed that statin therapy was associated with a notable decrease in all-cause mortality and major adverse cardiovascular events (MACE) in MINOCA cases.[40]

5.1.3. Beta-blockers

Beta-blockers are commonly prescribed post-MINOCA, especially when myocardial stress or ischemia is suspected. A meta-analysis conducted in 2022 found that beta-blocker therapy was associated with a 19% reduction in all-cause mortality (hazard ratio [HR]: 0.81; 95% confidence interval [CI]: 0.66–0.99).[41] However, more reliable and randomized evidence is still pending; the MINOCA-BAT trial is currently underway to evaluate how beta-blockers (and angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARBs]) affect this population's challenging clinical outcomes.[42]

5.1.4. ACEi/ARBs

In MINOCA patients, ACEi and ARBs are recommended. According to the SWEDEHEART registry study, ACEi/ARBs therapy was associated with a 22% reduction in mortality in MINOCA cases.[43] In addition, the Korean registry study reported a lower mortality rate in MINOCA patients who were prescribed ACEi/ARBs on discharge.[44]

5.1.5. Dual antiplatelet therapy (DAPT)

The efficacy of DAPT in MINOCA remains uncertain. A 2025 meta-analysis of seven studies (n = 12,307) showed a non-significant trend of decreased MACE with DAPT (HR: 0.82; 95% CI: 0.66–1.03).[45] Furthermore, registry data revealed that up to 55% of MINOCA patients are prescribed DAPT at discharge, though its clinical benefit remains uncertain.[46]

Recent studies suggest a role for cardioprotective agents, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, particularly in patients with left ventricular dysfunction following MI or those with cardiometabolic comorbidities. A 2025 meta-analysis demonstrated a 21% reduction in all-cause mortality among patients receiving SGLT2 inhibitors after MI, regardless of the timing of initiation.[47]

5.2. Etiology-specific management

5.2.1. Coronary vasospasm

Calcium-channel blockers, including dihydropyridines and non-dihydropyridines, are considered the first-line therapy to suppress vasospastic episodes.[48,49] Long-acting nitrates are also effective in relieving symptoms, though tolerance and endothelial dysfunction may develop.[50] In refractory cases, alternative agents such as nicorandil, cilostazol, magnesium, and Rho-kinase inhibitors (e.g., fasudil) have demonstrated therapeutic efficacy in small clinical trials.[49,50]

5.2.2. CMD

CMD is managed by improving endothelial function and alleviating ischemia. ACEI/ARBs and statins exhibit a vascular protective effect. Symptomatic relief can be achieved with beta-blockers, calcium channel blockers, and ranolazine, which, although supported by limited evidence, have shown benefits in reducing angina. In addition, other strategies, such as lifestyle modification, stress reduction, and cardiac rehabilitation, are also crucial for long-term symptom control.[27]

5.2.3. Plaque disruption (rupture/erosion)

Standard secondary prevention strategies are recommended for patients with plaque disruption detected on OCT or IVUS. DAPT with aspirin and purinergic receptor type Y, subtype 12 (P2Y12) inhibitor is advised for 12 months.[49] Moreover, high-intensity statins are used for plaque stabilization, while beta-blockers and ACEi are utilized in the presence of left ventricular dysfunction. Despite the absence of significant stenosis, these patients remain at risk for future cardiovascular events.[21]

5.2.4. Takotsubo syndrome

In Takotsubo syndrome, supportive treatment is primarily employed. Acute phase treatment includes beta-blockers, ACEi, and diuretics in the presence of heart failure.[51] Anticoagulation is recommended in cases with apical ballooning or severe left ventricular dysfunction. However, the routine use of antiplatelet agents or statins is discouraged unless there are coexisting cardiovascular risk factors.[52]

5.2.5. SCAD

As the majority of patients with SCAD heal spontaneously, conservative management is preferred for clinically stable patients.[49] In cases of ongoing ischemia or hemodynamic instability, invasive procedures, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting, may be necessary. Beta-blockers may reduce arterial wall stress and lower the risk of recurrence. According to the expert consensus from the American Heart Association, patients who do not undergo PCI or stenting should receive single antiplatelet therapy rather than dual therapy, whereas standard ACS antiplatelet protocols apply when intervention is performed. In addition, screening for fibromuscular dysplasia is advised in all cases.[53] Although pregnancy-associated SCAD is rare, it is a severe condition that presents with worse ACS outcomes compared to SCAD in non-pregnant individuals. The optimal management strategies for pregnancy-associated SCAD remain uncertain, underscoring the need for further research to develop evidence-based management guidelines for this condition.[54]

5.2.6. Myocarditis

Management of myocarditis includes supportive care and guideline-directed therapy. In cases of giant cell or autoimmune myocarditis, immunosuppressive therapy is utilized. Antithrombotic therapy is generally not required unless arrhythmias or thromboembolic complications are present. Exercise should be restricted until clinical remission is achieved, typically for at least one month, with a tailored approach to accelerate recovery[55] (Table 4).

5.3. Key differences in MINOCA management: ESC 2024 versus AHA/ACC 2025 guidelines

The European Society of Cardiology (ESC) 2024 guideline recommends secondary prevention for all MINOCA patients. According to the guideline, therapeutic agents such as aspirin, statins, ACEis, ARBs, and beta-blockers are recommended for most patients unless a specific reason precludes their use. The ESC recommends routine functional testing for conditions such as vasospasm and microvascular problems.[55]

The American Heart Association/American College of Cardiology (AHA/ACC) 2025 guideline recommends MINOCA treatment based on the exact cause. Aspirin and statins are recommended only if MINOCA is caused by plaque disruption or atherosclerosis. ACEis, ARBs, and beta-blockers are recommended based on each patient's condition, such as heart failure and high blood pressure. Advanced imaging techniques, such as CMR imaging and specific tests, are recommended to identify the cause of MINOCA.[56]

The ESC recommends a one-size-fits-all approach to protect all patients, while the AHA/ACC recommends a more individualized strategy, tailoring medicines and diagnostic tests to the patient's specific condition.

5.3.1. Cardiac rehabilitation

Exercise-based cardiac rehabilitation has been shown to significantly improve outcomes in MINOCA patients.

Table 4. Management strategies in MINOCA by etiology

Etiology	First-line therapy	Additional/Alternative options
Plaque disruption	DAPT (12 months), high-intensity statin[21]	β-blocker, ACEi if left ventricular dysfunction[21]
Vasospasm	Calcium-channel blocker[48]	Long-acting nitrate, nicorandil, fasudil[50]
CMD	ACEi/ARB, statin[27]	β-blocker, CCB, ranolazine; [27] lifestyle and rehabilitation
SCAD	Conservative management[53]	β-blocker, antiplatelet; [53] screen for fibromuscular dysplasia
Myocarditis	Supportive care[55]	Immunosuppression (for giant cell/autoimmune myocarditis), avoid antithrombotics if no risk[55]
Takotsubo	Supportive treatment (e.g., β-blocker and ACEi) [52]	Diuretics in cases with heart failure; anticoagulants in cases with severe left ventricular dysfunction[52]
Embolism/thrombosis	Anticoagulant[13]	Investigate for AF, thrombophilia workup[14]

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin receptor blockers; CCB: Calcium channel blocker; CMD: Coronary microvascular dysfunction; DAPT: Dual antiplatelet therapy; MINOCA: Myocardial infarction with non-obstructive coronary arteries; SCAD: Spontaneous coronary artery dissection.

In a randomized trial of 524 MINOCA patients assigned to a home-based exercise program group and a control group, the exercise group showed significantly higher physical health scores, along with approximately a 50% reduction in all-cause mortality and a 40% reduction in MACE over a 3-year follow-up, compared with controls.[57] These findings suggest that cardiac rehabilitation improves the quality of life and reduces adverse cardiovascular effects.

5.3.2. Prognosis and long-term follow-up

Previously, MINOCA was regarded as a benign condition, but it is now recognized to be associated with adverse cardiovascular outcomes. The 12-month incidence of MACE varies between 4% and 15%, and recurrent chest pain, rehospitalization, and reinfarction are not uncommon. Female patients constitute the majority of MINOCA cases and often experience a greater symptom burden and higher psychosocial distress. Prognosis is poor in patients with reduced left ventricular ejection fraction, evidence of myocardial damage on CMR imaging, or myocarditis. Thus, individualized risk assessment is crucial for long-term management.[3]

Close follow-up is essential to detect recurrence, optimize secondary prevention, and identify evolving pathology. Repeat CMR imaging or echocardiography may be indicated in patients with initial myocardial damage, persistent symptoms, or unknown etiology. Women, in particular, should receive regular follow-ups due to the increased frequency of angina, psychological stressors, and potential under-treatment. Further management should include risk factor control, adherence monitoring, and screening for anxiety or depression. A multidisciplinary approach is recommended to improve both physical and emotional recovery.[43]

5.4. Gaps in evidence and future directions

There is a growing need for randomized controlled trials specifically targeting MINOCA subtypes, such as vasospasm, microvascular dysfunction, and plaque disruption. Such studies are essential to identify effective therapies and to avoid the application of management plans designed for obstructive MI populations.

The role of advanced imaging also warrants further investigation. While modalities such as intracoronary OCT and CMR imaging have proven valuable for diagnosis, current evidence does not confirm that imaging-guided therapy improves clinical outcomes. Emerging biomarkers represent another promising frontier. Although their clinical utility remains under study, novel biomarkers such as GDF-15, copeptin, and soluble ST2 show promise in improving risk stratification and guiding individualized therapy in MINOCA.[2]

6. Conclusion

As a diverse and clinically relevant syndrome, MINOCA has proven to be a challenge to conventional diagnostic and therapeutic approaches. Multiple mechanisms, such as coronary vasospasm, microvascular dysfunction, and plaque disruption, are involved in its pathophysiology. Accurate diagnosis depends on the integration of advanced imaging techniques, such as CMR imaging and intracoronary OCT, along with thorough clinical assessment.

Management should be individualized based on the underlying etiology. While general medical therapy may benefit many patients, targeted therapies, such as vasodilators for spasm or conservative care in SCAD, are crucial. Outcomes can be further optimized through cardiac rehabilitation, long-term follow-up, and psychosocial support.

Despite extensive research in understanding MINOCA, significant knowledge gaps remain. Therefore, future studies, such as randomized clinical trials, should focus on specific MINOCA subtypes, the impact of imaging-guided therapies, and the clinical utility of emerging biomarkers. Such efforts will advance diagnostic accuracy, refine therapeutic strategies, and ultimately enhance prognosis in this frequently neglected population.

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The authors declare they have no competing interests.

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