



State-of-the-Art Review

Myocardial infarction with non-obstructive coronary arteries (MINOCA): State-of-the-Art Review

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The working diagnosis of Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) is a heterogeneous clinical entity that includes true ischemic etiologies and MINOCA mimickers, and accounts for approximately 4-15% of all acute myocardial infarctions (MI). The underlying ischemic etiologies are diverse, ranging from atherosclerotic plaque disruption to non-atherosclerotic mechanisms such as coronary artery spasm, coronary microvascular dysfunction, spontaneous coronary artery dissection, and coronary thrombosis or embolism. Although the risks of all-cause mortality and recurrent cardiac events are lower than in MI with obstructive coronary artery disease (MI-CAD), patients with MINOCA remain at significantly increased risk of adverse outcomes compared with the general population. Accurate diagnosis remains challenging due to overlapping clinical features with MINOCA mimickers and the lack of standardized diagnostic algorithms. Advanced imaging modalities, particularly early cardiac magnetic resonance imaging and intracoronary imaging techniques including optical coherence tomography and intravascular ultrasound, significantly enhance diagnostic precision by enabling detailed myocardial tissue characterization and identification of culprit lesions. However, management strategies remain controversial due to the absence of large randomized controlled trials dedicated to MINOCA and different underlying etiologies, resulting in treatment approaches that are mainly extrapolated from studies on MI-CAD and observational registry data. Standard MI therapies should not be uniformly applied to all patients with MINOCA; instead, management should be individualized according to the underlying mechanism. Future research should prioritize large-scale, mechanism-specific randomized trials, the validation of standardized diagnostic pathways, and the integration of multimodal imaging into routine clinical practice to improve outcomes for this diverse patient population.



Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) refers to patients presenting with acute myocardial injury and clinical features of acute myocardial infarction (MI), but without significant obstructive coronary artery disease (CAD) on coronary angiography.^{1,2} The reported prevalence of working diagnosis of MINOCA varies, ranging from 4% to 15%.^{1,3} Compared to patients with classical MI due to obstructive CAD (MI-CAD), those with MINOCA tend to be younger, female, and less likely to have traditional cardiovascular risk factors such as dyslipidemia.^{3,4}

Historically, MINOCA was often considered a false-positive diagnosis; however, advances in cardiac imaging and biomarker studies have confirmed that true myocardial injury can occur in the absence of obstructive CAD. Current guidelines now recognize MINOCA as a working diagnosis that warrants further investigation to identify the underlying etiology.^{1,2} This approach is critical, as

MINOCA is associated with a significantly increased risk of adverse outcomes compared with the general population, and its prognosis is not as benign as initially believed.⁵ Moreover, identifying the underlying etiology is essential, as the causes of MINOCA are heterogeneous and the appropriate management can vary substantially depending on the specific diagnosis.^{3,6,7,8}

A large prospective cohort study of 900 patients with MINOCA demonstrated that although the risk of all-cause mortality and recurrent MI was lower than in MI-CAD patients, MINOCA patients still had a 4.6-fold higher risk of composite outcomes compared to age-matched controls without cardiovascular disease.⁶ Another large cohort study showed that MINOCA has a prognosis similar to single vessel MI-CAD in terms of morbidity and cause-specific mortality in first-time MINOCA.⁹ Similarly, the SWEDEHEART registry, which included 9,000 MINOCA patients, reported a 13.4% all-cause mortality and a 24% incidence of major adverse cardiovascular events (MACE) at 4 years.⁷ The CathPCI registry,

which included over 16,000 MINOCA patients aged ≥ 65 years, showed a 12.3% 1-year mortality and an 18% MACE rate.⁸ More recently, a retrospective cohort study reported similar long-term all-cause mortality between patients with true MINOCA and those with MI-CAD, whereas mortality was significantly lower among patients with nonischemic MINOCA mimickers.¹⁰ These findings underscore the need for careful diagnostic evaluation and tailored management in MINOCA patients.¹¹ This review aims to summarize the current understanding of the pathophysiology, diagnostic approach, and therapeutic evidence of MINOCA to guide clinical evaluation and management. By integrating the Fifth Universal Definition of MI with emerging randomized evidence, this review provides a contemporary framework for transitioning from an initial working diagnosis of MINOCA to definitive etiologic classification and mechanism-directed treatment. The search criteria with keywords of myocardial infarction with non-obstructive coronary arteries, MINOCA, coronary microvascular dysfunction, coronary vasospasm, and spontaneous coronary artery dissection were used to collect reports published in English language only in the PubMed database from its inception to August 2025. A targeted search update through October 2026 incorporated recent evidence. Studies were selected based on clinical relevance, prioritizing landmark studies, randomized trials, large observational studies, systematic reviews, and contemporary society guidance.

Definition of MINOCA

Traditionally, MINOCA was defined by three essential criteria: (1) fulfillment of the universal definition of acute MI; (2) absence of obstructive CAD, typically defined as no stenosis $\geq 50\%$ in any major epicardial vessel on coronary angiography; and (3) no clinically overt alternative explanation for the presentation.^{1,2} Under the Fourth Universal Definition of MI, the diagnosis of MINOCA required evidence of myocardial injury accompanied by clinical signs of myocardial ischemia.¹² More recently, the Fifth Universal Definition of MI updated the definition of MINOCA to myocardial injury with non-obstructive coronary arteries, emphasizing that MINOCA rep-

resents a working rather than a final diagnosis.¹³ This updated terminology recognizes that subsequent evaluation may identify either an ischemic MI mechanism or an alternative cardiac or non-cardiac cause of myocardial injury. When MI is subsequently confirmed, the final diagnosis should be classified as primary, secondary, or procedure-related MI according to the underlying clinical setting.¹³

Because elevated troponin levels may result from both ischemic and non-ischemic mechanisms, distinguishing true MINOCA from other causes of myocardial injury is essential.¹¹ Non-ischemic conditions, such as myocarditis, Takotsubo syndrome, sepsis, pulmonary embolism, or cardiac trauma, may mimic acute MI.¹² These “MINOCA mimickers” must be systematically excluded before confirming the diagnosis.^{1,2} Therefore, MINOCA should be considered an initial working diagnosis at the time of coronary angiography, prompting further evaluation to distinguish primary MI due to acute coronary pathology, secondary MI due to another acute condition, and alternative nonischemic causes of myocardial injury.^{1,2,13}

The diagnostic process begins when a patient presents with a clinical picture consistent with acute MI but without significant obstructive CAD on angiography. At this stage, it is crucial to exclude overt non-coronary causes of myocardial injury and to ensure that subtle obstructive lesions, especially in distal vessels or complete occlusions in small segments, are not overlooked.¹ Left ventricular angiography may also be useful at the time of coronary angiography, as it can identify wall-motion abnormalities and suggest the diagnosis of Takotsubo syndrome. Cardiac magnetic resonance imaging (CMR) plays a central role in this evaluation, as it can identify non-ischemic injury patterns such as myocarditis or Takotsubo syndrome, and confirm ischemic injury when present.^{1,2} The diagnostic algorithm is presented in Figure 1.

Ultimately, suspected MINOCA represents a heterogeneous clinical syndrome encompassing both ischemic and non-ischemic etiologies, whereas true MINOCA reflects confirmed ischemic mechanisms [1, 2]. The pathophysiology is summarized in Figure 2. Identifying the precise underling

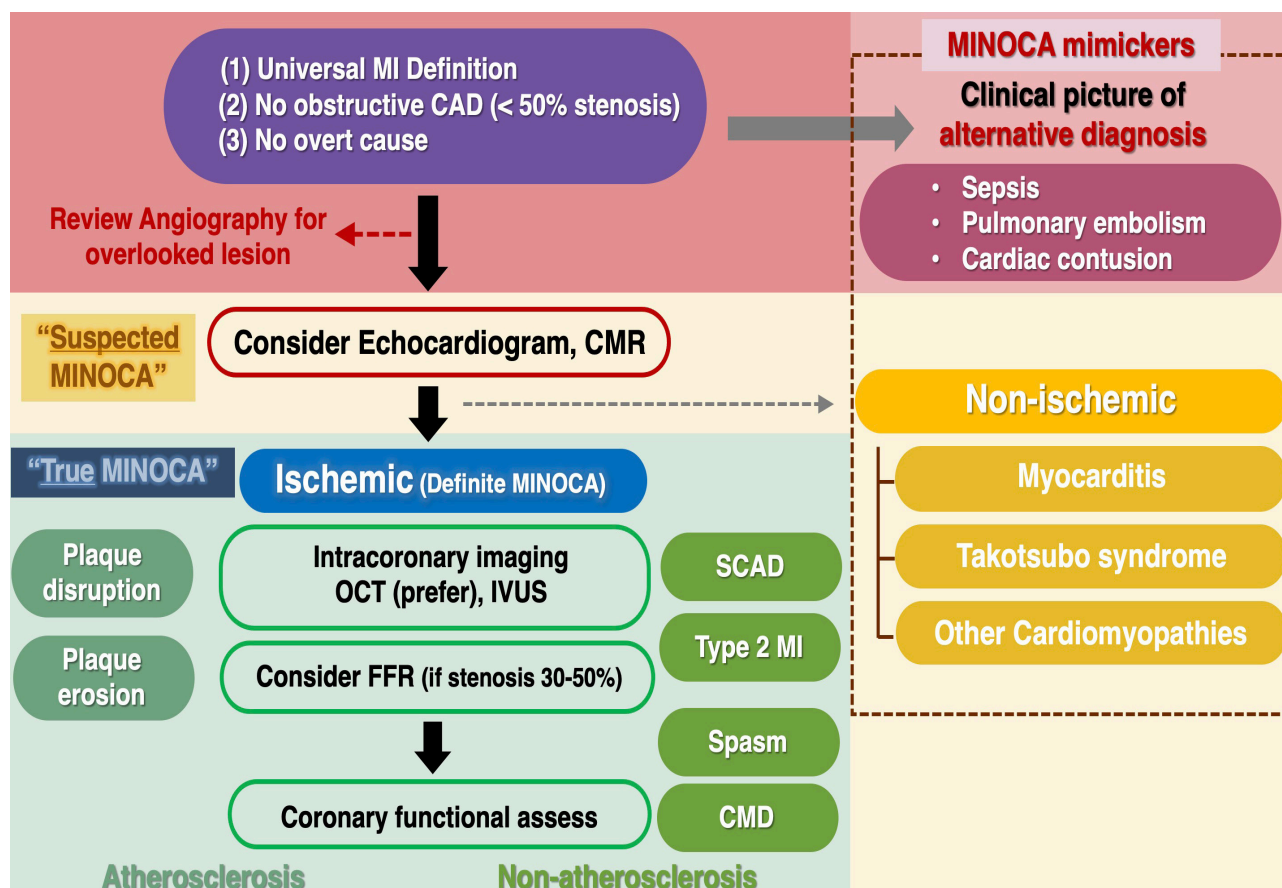


FIGURE 1. Diagnostic algorithm for patients with suspected myocardial infarction with non-obstructive coronary arteries (MINOCA). The flowchart outlines a stepwise evaluation, beginning with the exclusion of MINOCA mimickers, differentiation between ischemic and non-ischemic etiologies, and the use of advanced non-invasive and invasive imaging modalities to identify the underlying cause. CAD coronary artery disease; CMD coronary microvascular dysfunction; CMR Cardiac magnetic resonance imaging; FFR fractional flow reserve; IVUS intravascular ultrasound; MI myocardial infarction; OCT optical coherence tomography.

mechanism is critical, as it directly informs both management strategies and long-term prognosis.

Atherosclerotic Causes of MINOCA

Atherosclerosis is a major underlying mechanism in a substantial proportion of MINOCA patients. Risk factors associated with different mechanisms of MINOCA are summarized in Table 1.^{14,15,16,17,18} The pathophysiology involves plaque disruption, which includes plaque rupture, plaque erosion, and calcified nodules.¹ These disruptions can trigger thrombus formation, leading to myocardial injury through mechanisms such as distal embolization, transient coronary occlusion, or luminal narrowing, which may be exacerbated by concurrent coronary vasospasm.¹ Spontaneous thrombolysis can result in non-obstructive findings on coronary angiography despite clear evidence of myocardial ischemia.¹

Table 1. Mechanism-specific pharmacological strategies for MINOCA

Importantly, coronary atherosclerosis contributes to MINOCA through several non-obstructive mechanisms beyond focal epicardial stenosis. Atherosclerotic plaque erosion can lead to distal coronary microembolization, resulting in patchy microinfarction, microvascular obstruction, and release of particulate debris and inflammatory mediators that impair the microcirculation despite angiographically normal-appearing arteries.^{19,20} In addition, diffuse atherosclerotic remodeling and endothelial dysfunction can reduce coronary flow reserve and contribute to microvascular dysfunction.²⁰ Thus, atherosclerosis in MINOCA encompasses a spectrum of epicardial and microvascular processes rather than solely obstructive disease. Advanced intracoronary imaging modalities, including optical coherence tomography (OCT) and

TABLE 1. Mechanism-specific pharmacological strategies for MINOCA

CAUSE OF MINOCA	PHARMACOLOGICAL STRATEGIES	SUPPORTING EVIDENCE
Atherosclerosis	Antiplatelet therapy (SAPT/DAPT), statin	AHA scientific statement; observational MINOCA registry evidence; DAPT benefit remains uncertain.
Epicardial spasm	CCBs, nitrates	AHA scientific statement; evidence extrapolated from randomized and observational studies in vasospastic angina; long-acting nitrate benefit remains uncertain.
Microvascular dysfunction	Beta-blockers, CCBs, nitrates	AHA scientific statement; evidence extrapolated from small randomized studies of INOCA/microvascular angina; MINOCA-specific treatment trials are lacking.
SCAD	Antiplatelet therapy (SAPT/DAPT), beta-blockers	AHA scientific statement; randomized treatment evidence is lacking; observational evidence supports beta-blockers; the optimal antiplatelet strategy remains uncertain.
Coronary embolism	Anticoagulation	AHA scientific statement; expert opinion; MINOCA-specific randomized treatment evidence is lacking.
Undefined	Antiplatelet therapy, statin, beta-blockers, ACEI/ARB	AHA scientific statement; observational MINOCA registry evidence; benefits of routine treatment remain uncertain.

ACEI angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; CCBs calcium channel blockers; DAPT dual

intravascular ultrasound (IVUS), have enhanced the detection of plaque disruption in MINOCA, especially when conventional angiography fails to identify a culprit lesion.^{21,22,23,24} Among selected MINOCA patients undergoing OCT or IVUS, plaque disruption was identified in approximately 24% to 40% of cases, although definitions varied across studies.^{21,22,23} For instance, the HARP multicenter study identified OCT-detectable atherosclerotic lesions in 43% of women with MINOCA.²¹ Notably, up to 30% of patients with angiographically normal coronary arteries were found to have a clear culprit lesion on OCT, highlighting the limitations of conventional angiography and the usefulness of intracoronary imaging.²¹ Similarly, plaque disruption was noted among 37% of patients on IVUS in a study from Paris that enrolled MINOCA patients.²⁵ Comparative studies reveal distinct differences in plaque morphology between MINOCA and MI-CAD. Plaque erosion, characterized by thrombus forma-

tion on an irregular endothelial surface with an intact fibrous cap, is more frequently observed in MINOCA compared to MI-CAD. The MINOCA characteristics of OCT features of erosions are a thick intima and a small or absent lipid core. If the lipid core is present, it does not communicate with luminal thrombi.²⁶ Calcified nodules, although less common, can also lead to thrombotic events.²⁷ Vulnerable plaques with thin-cap fibroatheromas are significantly less common in MINOCA (3%) compared to MI-CAD (35%). In contrast, intraplaque hemorrhage (47% in MINOCA vs. 2% in MI-CAD) and layered plaques (31% in MINOCA vs. 12% in MI-CAD) are more frequently observed in MINOCA.²⁷ An OCT study of 99 MINOCA patients reported plaque erosion in 65%, plaque rupture in 33%, and calcified nodules in 2%.²⁴ Among women presenting with MINOCA, Iqbal and colleagues found that plaque disruption occurred in fibrous or fibrofatty plaques and, contrary to expectations, was not typically

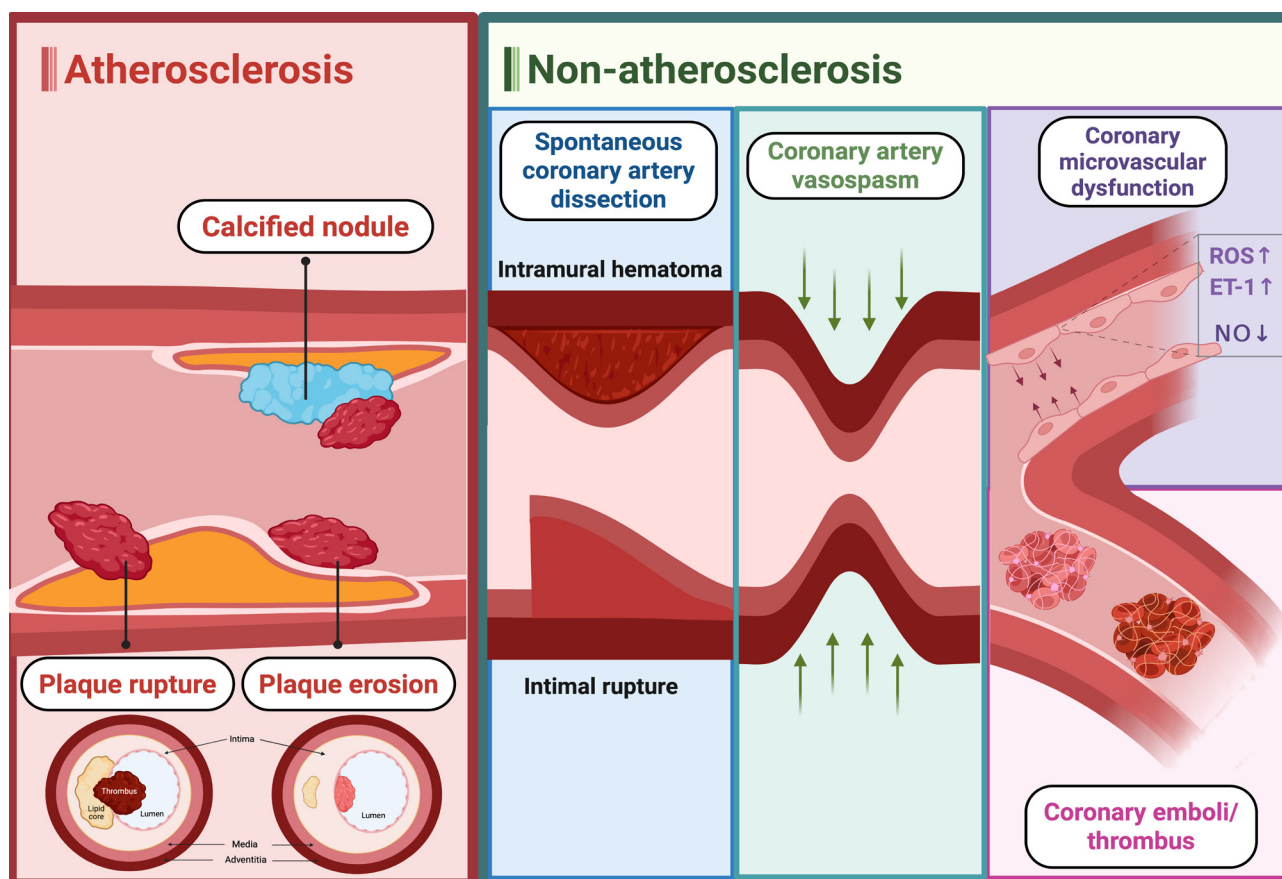


FIGURE 2. Pathophysiological mechanisms of myocardial infarction with non-obstructive coronary arteries (MINOCA), encompassing both atherosclerotic and non-atherosclerotic etiologies. The schematic illustrates key processes, including plaque rupture, plaque erosion, coronary vasospasm, coronary microvascular dysfunction, spontaneous coronary artery dissection, and coronary embolism/thrombosis. Created in BioRender. Attachaipanich, T. (2026) <https://BioRender.com/n5wa4gb>. ET-1 endothelin-1; NO nitric oxide; ROS reactive oxygen species; VSMCs vascular smooth muscle cells.

seen in eccentric, outwardly remodeled, or soft plaques.²⁸

Collectively, these findings suggest that plaque erosion is more common in MINOCA, while plaque rupture predominates in MI-CAD. When plaque rupture does occur, its characteristics differ from those noted in MI-CAD. The use of intracoronary imaging is critical in detecting subtle atherosclerotic lesions that may be missed by angiography. Identifying plaque disruption in MINOCA supports the use of secondary prevention strategies similar to those for MI-CAD. Based on current evidence, several limitations should be acknowledged. Most studies investigating plaque morphology in MINOCA rely on small OCT or IVUS cohorts, often conducted at tertiary centers with inherent selection bias. Comparator groups, such as chest pain patients without myo

cardial injury, are rarely included, making it difficult to determine the true prevalence of plaque disruption in MINOCA. Furthermore, many studies do not systematically exclude mimickers with CMR or fully assess non-atherosclerotic etiologies, contributing to the variation in reported prevalence of plaque morphology across studies.

Non-atherosclerotic Causes of MINOCA

In addition to atherosclerotic mechanisms, several non-atherosclerotic conditions have been identified as causes of definitive MINOCA. Recognizing these mechanisms is clinically significant, as cohort studies have shown that patients with MINOCA due to non-atherosclerotic etiologies experience similar risks of composite outcomes, including all-cause mortality and recurrent MI, over two years, com-

pared to those with mild CAD.⁶

Epicardial Coronary Vasospasm

Coronary vasospasm is a common non-atherosclerotic cause of MINOCA, with prevalence estimates ranging widely from 4% to 65%, depending on the population, diagnostic protocols, and use of provocative testing.²⁹ Importantly, vasospasm often occurs concomitantly with underlying atherosclerotic disease.³⁰ A meta-analysis reported a pooled prevalence of approximately 40%, though true prevalence remains uncertain, as provocation testing is not routinely performed and is typically reserved for selected patients.³¹

Epicardial vasospasm can cause transient near-complete coronary occlusion, resulting in ischemia despite the absence of obstructive CAD. It may also exacerbate ischemia in the presence of pre-existing, non-severe plaque disruption.¹ Coronary vasospasm is defined as transient $\geq 90\%$ coronary constriction, accompanied by angina and ischemic ECG changes, either spontaneously or after pharmacologic provocation.³² Invasive provocation testing with intracoronary acetylcholine or ergonovine is the diagnostic gold standard, with inducible spasm observed in 28% to 65% of tested MINOCA patients.^{3,32,33,34}

Vasospasm is more prevalent in females and in Asian populations. Japanese studies report inducible spasm in up to 81% of MINOCA cases, compared to lower rates in Europe and the United States.^{3,35} Moreover, in patients with MI-CAD, Japanese individuals were found to have a threefold higher incidence of inducible vasospasm compared with Caucasians.³⁶ Recurrent or rest angina, typically occurring in the early morning, may suggest vasospastic angina.^{37,38} Importantly, many patients with inducible vasospasm also show evidence of non-obstructive CAD on angiography.³⁴ Predictors of coronary spasm include younger age, typical chest pain, prior angina, ST-segment elevation, and lower left ventricular ejection fraction (LVEF).³⁹

The timing of provocation testing can influence detection rates. In MI-CAD populations, testing within six weeks of MI increases the likelihood of inducible spasm compared to testing later.³⁰ An

earlier systematic review in MINOCA patients demonstrated that inducible spasm is present in approximately 28% of those tested within six weeks after an MI, comparable to the 34% observed when testing is performed beyond six weeks.³ However, more recent studies that performed early provocation testing, often immediately after coronary angiography, reported higher rates of inducible spasm in MINOCA, ranging from 46% to 58%.^{33,34} These findings suggest that the timing of provocation testing may significantly affect detection rates in MINOCA, as previously observed in MI-CAD; however, they may also merely reflect differences in cohort compositions. Nevertheless, direct evidence comparing early versus late testing remains limited, and further controlled studies are needed to clarify the impact of timing.

Overall, the evidence for vasospasm in MINOCA remains limited by methodological challenges. Most data are derived from highly selected cohorts, and findings vary depending on the heterogeneity of MINOCA populations, the timing of evaluation, and the provocation testing protocols used. The absence of standardized testing approaches and suitable control groups further contributes to uncertainty in defining its true prevalence and clinical impact.

Coronary Microvascular Dysfunction (CMD)

A meta-analysis reported a pooled prevalence of CMD in approximately 41% of MINOCA patients.³¹ When combined with epicardial coronary vasospasm, coronary vasomotor dysfunction was present in up to 49% of cases, highlighting its substantial role in MINOCA.³¹ Similar to epicardial coronary spasm, CMD is more prevalent in females.³¹

CMD arises from structural and functional abnormalities in the coronary microcirculation, resulting in impaired coronary blood flow and subsequent myocardial ischemia.⁴⁰ The coronary microvasculature, which contributes up to 60% of total coronary vascular resistance, plays a critical role in regulating blood flow to meet myocardial oxygen demand, particularly since myocardial oxygen extraction is already near maximal at rest.⁴⁰

CMD results from endothelial dysfunction or vas-

cular smooth muscle hyperreactivity, resulting in reduced vasodilation and enhanced vasoconstriction.⁴⁰ Additional mechanisms include extrinsic compression of intramural vessels, microvascular spasm and inflammation.¹ Microvascular spasm is characterized by angina and ischemic ECG changes during provocative testing without epicardial spasm, whereas impaired microvascular vasodilator capacity is reflected by reduced coronary flow reserve (CFR) and/or elevated index of microvascular resistance (IMR).

Coronary Embolism, Thrombosis, and Thrombophilia

Coronary embolism or thrombosis may cause MINOCA by occluding microvasculature or epicardial arteries, often with partial thrombus lysis. These mechanisms occur independently of atherosclerotic plaque or obstructive CAD and are often associated with underlying hypercoagulable states.¹ Criteria for the diagnosis of coronary embolism by Shibata et al.⁴¹

Other acquired thromboembolic causes include left ventricular thrombus, valvular heart disease, prosthetic heart valves, infective endocarditis, atrial fibrillation, pulmonary embolism, cardiac myxoma, papillary fibroelastoma, and cancer-associated thrombophilia. The estimated prevalence of MI due to coronary embolism is approximately 2.9%.⁴¹ Coronary embolism can be diagnosed using the proposed Shibata criteria, which categorize findings into major and minor components.⁴¹ These criteria integrate angiographic features and clinical clues suggestive of an embolic rather than plaque-mediated mechanism. Major criteria include angiographic evidence of embolism without significant atherosclerosis, coronary embolization at multiple sites, and concomitant systemic embolism. Minor criteria include the absence of diffuse coronary artery disease, identification of an embolic source, and the presence of embolic risk factors. Definite coronary embolism is diagnosed when ≥ 2 major criteria, or 1 major plus ≥ 2 minor criteria, or ≥ 3 minor criteria are met.⁴¹

MAJOR CRITERIA

Angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components

Concomitant coronary artery embolization at multiple sites*

Concomitant systemic embolization without left ventricular thrombus attributable to acute myocardial infarction

MINOR CRITERIA

<25% stenosis on coronary angiography, except for the culprit lesion

Evidence of an embolic source based on transthoracic echocardiography, transesophageal echocardiography, computed tomography, or MRI

Presence of embolic risk factors: atrial fibrillation, cardiomyopathy, rheumatic valve disease, prosthetic heart valve, patent foramen ovale, atrial septal defect, history of cardiac surgery, infective endocarditis, or hypercoagulable state

Definite CE

Two or more major criteria, or One major criterion plus ≥ 2 minor criteria, or Three minor criteria

Probable CE

One major criterion plus 1 minor criterion, or Two minor criteria

A diagnosis of CE should not be made if there is

Pathological evidence of atherosclerotic thrombus

History of coronary revascularization

Coronary artery ectasia

Plaque disruption or erosion detected by intravascular ultrasound or optic coherence tomography in the proximal part of the culprit lesion

CE: Coronary artery Embolism, MRI: Magnetic Resonance Imaging. *indicates multiple vessels within 1 coronary artery territory or multiple vessels in the coronary tree.

A meta-analysis of 378 MINOCA patients undergoing partial thrombophilia screening showed that approximately 14% had inherited thrombotic disorders.³ The most common abnormalities included Factor V Leiden mutation, present in about 12% of MINOCA patients, which is higher than the 3% to 7% prevalence reported in the general population. Protein C and protein S deficiencies were also observed in 2.6% of MINOCA patients, compared to 0.1% to 1% in the general population.^{3,42}

The prevalence of thrombophilia appears higher in MINOCA than in MI-CAD. One study reported Factor V Leiden mutation in 5% of patients with MI-CAD.⁴³ Similarly, a study of 84 MINOCA patients undergoing comprehensive testing reported abnormalities in 24%, a prevalence comparable to that of patients with cryptogenic stroke.⁴⁴ In this cohort, Factor V Leiden mutation was found in 14%, antiphospholipid syndrome in 15.5%, and activated protein C resistance in 2.4%.⁴⁴ Importantly, the majority of studies reporting a higher prevalence of Factor V Leiden were conducted in European cohorts, where the background prevalence of this mutation is known to be higher. Antiphospholipid syndrome prevalence in the general population ranges from 1% to 5%, reaching up to 11% in MI patients.⁴⁵ Furthermore, among MI patients who tested positive for antiphospholipid antibodies, approximately 20% were diagnosed with MINOCA.⁴⁶ However, these estimates should be interpreted cautiously due to differences in patient selection, screening methods, and background prevalence.

These findings highlight the importance of thrombophilia evaluation in selected MINOCA populations, particularly in younger individuals without conventional cardiovascular risk factors.

Spontaneous Coronary Artery Dissection (SCAD)

SCAD is an uncommon but increasingly recognized cause of MI, particularly among younger women without traditional cardiovascular risk factors.^{1,18} SCAD is defined as a spontaneous dissection of the epicardial coronary artery unrelated to atherosclerosis, trauma, or iatrogenic injury.¹⁸ Myocardial injury results from coronary obstruction caused by intramural hematoma or intimal disruption, caus-

ing significant narrowing, although some cases with less severe narrowing fall within the MINOCA spectrum.¹⁸

The true prevalence of SCAD remains uncertain due to underdiagnosis and challenges in recognition. SCAD accounts for approximately 1% to 4% of all ACS, but up to 35% in women under 50 years old presenting with ACS.¹⁸ Coronary angiography is the initial diagnostic modality, with three angiographic types including type 1 (double lumen with contrast staining), type 2 (long diffuse narrowing), and type 3 (focal narrowing resembling atherosclerosis).^{18,47} In the SCAD registry, type 2 lesions are the most common (67%), followed by type 1 (29%) and type 3 (4%).⁴⁷ Notably, no significant differences in outcomes exist between these subtypes.⁴⁷

Because SCAD may be missed or misinterpreted on angiography, particularly in cases of type 2 or type 3 patterns, intravascular imaging with IVUS or OCT may be required to confirm the diagnosis. These imaging modalities can demonstrate the absence of atherosclerotic plaque and confirm the presence of dissection and intramural hematoma. In MINOCA patients, 4% to 7% of cases diagnosed by IVUS or OCT revealed SCAD with <50% luminal stenosis.^{24,48,49} However, both IVUS and OCT carry procedural risks, as wire passage may propagate dissection and OCT contrast injection may extend intramural hematoma. Current guidelines therefore recommend their use selectively, only when the diagnosis is uncertain and the results are expected to alter management.^{18,50} In one study of 63 SCAD patients who underwent OCT, 7.9% experienced OCT-related complications, although none resulted in MACE.⁵¹ Overall, intravascular imaging is considered safe and can be valuable in cases of diagnostic uncertainty. There are increasing data on the use of coronary computed tomography angiography (CCTA) in SCAD.^{18,50} As a non-invasive tool, CCTA can visualize coronary anatomy, but evidence supporting its role in acute diagnosis remains limited. Current guidelines recommend its use mainly for longitudinal monitoring or when angiographic findings are inconclusive, rather than as a first-line modality in the acute setting.^{18,50}

Oxygen Supply-Demand Mismatch

An imbalance between myocardial oxygen supply and demand can lead to myocardial ischemia and, when diagnostic criteria are fulfilled, infarction, historically classified as type 2 MI.¹² This mismatch may result from increased oxygen demand (e.g., tachyarrhythmias, severe hypertension) or reduced oxygen supply (e.g., hypoxia, anemia, hypotension).⁵²

While various mechanisms contribute to supply-demand mismatch, most cases are triggered by non-coronary etiologies that affect systemic oxygen delivery or myocardial demand. The presence and severity of concomitant CAD may modulate the ischemic threshold. Under the previous Universal Definition of MI classification, type 2 MI could also result from direct impairment of coronary blood flow, such as in vasospasm, coronary embolism, or SCAD.⁵² Notably, the Fifth Universal Definition of MI replaces the previous numerical MI classification with primary, secondary, and procedure-related MI; acute coronary pathologies such as vasospasm, coronary embolism, and SCAD are now classified as causes of primary MI, whereas secondary MI refers to myocardial oxygen supply-demand imbalance resulting from another acute condition.¹³ Intravascular imaging (IVUS, OCT) can detect subtle or diffuse coronary abnormalities not visible on angiography, including non-obstructive plaques that may contribute to ischemia under increased demand.¹ Therefore, systemic causes of supply-demand mismatch identified during the evaluation of suspected MINOCA should be considered alternative diagnoses rather than primary coronary mechanisms of MINOCA. Recognizing this distinction is essential, as management should focus on treating the underlying precipitating condition.

Sex Differences in MINOCA

Relative to obstructive CAD, which is more common in men, the prevalence of suspected MINOCA is disproportionately higher in women.^{53,54,55} Data from large registries report that in STEMI patients, 4% to 9% of women have non-obstructive CAD compared to 2% to 8% of men.^{56,57} In NSTEMI, 10% to 15% of women compared with 4% to 5% of men

have non-obstructive CAD.^{56,57} Although fewer than half of MI-CAD patients are women, they represent 37% to 77% of MINOCA cases.^{53,54} In a cohort study of MI patients, women had five times higher odds of having MINOCA compared with men.⁵⁸ Similarly, in NSTEMI patients undergoing coronary angiography, female sex was identified as an independent predictor of MINOCA.⁵⁹ Among women with MINOCA, only about 14% present with STEMI, but this subgroup has a higher risk of adverse outcomes.⁵³

For non-atherosclerotic causes of MINOCA, women are more susceptible to CMD.⁵⁴ SCAD shows a marked female predominance, with only 8% to 10% of cases occurring in men. SCAD may be responsible for up to 35% of younger women presenting with ACS, compared to 1% to 4% of all overall ACS cases.¹⁸ Pregnancy-associated SCAD is the leading cause of MI during pregnancy or the postpartum period and is associated with a poorer prognosis compared with non-pregnancy-related SCAD.⁶⁰

Preliminary molecular studies suggest a potential role of estrogen signaling in sex differences in MINOCA. In a transcriptomic study of 11 women with MINOCA, estrogen receptor signaling emerged as the most differentially regulated pathway compared to MI-CAD patients and controls.⁶¹ G-protein-coupled estrogen receptor (GPER), the most abundant estrogen receptor transcript, along with several other estrogen-related genes, showed reduced expression in MINOCA, suggesting impaired estrogen-mediated cardioprotective effects.⁶¹ These observations underscore the potential influence of hormonal pathways, although larger studies including male patients are needed to clarify the underlying mechanisms.

However, the influence of estrogen alone is unlikely to fully explain the female predominance of MINOCA, particularly given that the established cardiovascular effects of estrogen primarily modulate atherosclerotic rather than non-atherosclerotic processes.

Beyond hormonal influences, sex-specific differences in coronary anatomy and physiology also contribute to the higher prevalence of MINOCA observed in women. Women tend to have smaller

epicardial coronary arteries, higher resting and hyperemic myocardial blood flow, and greater endothelial shear stress compared with men, features that promote diffuse epicardial atherosclerosis and microvascular dysfunction rather than focal obstructive plaque formation.^{53,62} These observations support a pathophysiologic framework in which sex-related variations in coronary size, flow dynamics, and vascular reactivity predispose women to non-obstructive ischemic mechanisms characteristic of MINOCA.

The effect of sex on long-term MINOCA outcomes remains unclear. Data from large registries have shown that sex is not an independent predictor of adverse outcomes.^{7,8} Similarly, a meta-analysis found no significant differences in all-cause mortality or MACE between sexes.⁶³ However, a recent retrospective study of 6,000 MINOCA patients reported lower mortality and MI rates in women compared to men at 3-year follow-up.⁶⁴ Evidence on sex-specific treatment effects is limited. In a propensity-matched analysis, statins and ACEI/ARBs were associated with reduced MACE in both sexes.⁷ Beta-blockers showed a trend toward benefit, while dual antiplatelet therapy (DAPT) showed no clear advantage, with findings consistent across both sexes.⁷

Biomarkers in MINOCA

The identification and interpretation of circulating biomarkers play a crucial role in the evaluation of patients hospitalized with acute MI. Although MINOCA shares some clinical and biochemical features with MI-CAD, emerging evidence suggests distinct pathophysiological mechanisms that may be reflected in differing biomarker profiles.⁶⁵ However, a comprehensive and specific biochemical signature for MINOCA remains to be clearly defined.

Cardiac Troponins

Cardiac troponins (cTnI and cTnT), particularly measured with high-sensitivity assays (hs-cTn), are the cornerstone biomarkers for myocardial injury, with levels exceeding the 99th percentile diagnostic

threshold.¹² In MINOCA, elevated troponin concentrations are a requisite criterion; however, clinical interpretation demands exclusion of alternative diagnoses such as myocarditis, Takotsubo cardiomyopathy, or renal impairment.¹ Compared to MI-CAD, hs-cTn release in MINOCA typically exhibits a less pronounced and more protracted elevation, reflecting distinct injury patterns.^{66,67} Despite these kinetic differences, troponin dynamics alone do not reliably discriminate underlying mechanisms, underscoring the necessity for comprehensive multimodal evaluation.

Inflammatory Biomarkers

Inflammation is increasingly recognized as a pivotal component of MINOCA pathogenesis. Elevated C-reactive protein (CRP), including high-sensitivity CRP (hs-CRP), is frequently documented during the acute phase and correlates with adverse outcomes such as all-cause mortality and MACE.⁶⁸ However, comparative studies frequently report overlapping CRP levels between MINOCA and MI-CAD populations, limiting its discriminative power.^{67,69} More specific inflammatory mediators, such as interleukin-6 (IL-6), P-selectin glycoprotein ligand-1 (PSGL-1), and NF- κ B essential modulator (NEMO), are elevated in MINOCA patients, indicating amplified inflammatory signaling.^{65,70} Longitudinal studies reveal persistent elevation of vascular injury markers including soluble vascular cell adhesion molecule-1 (sVCAM-1), CCL-21, and placental growth factor (PIGF) up to one year post-infarction, suggesting ongoing endothelial dysfunction and microvascular injury.^{71,72} Notably, adipokines like visfatin, secreted by visceral adipose tissue, have emerged as potential mediators of endothelial impairment and inflammatory-metabolic dysregulation.⁷³ Despite accumulating evidence, inflammatory biomarker profiling remains investigational and is not yet integrated into routine clinical risk stratification or management algorithms for MINOCA.

Natriuretic Peptides

N-terminal pro-B-type natriuretic peptide (NT-proBNP), reflecting myocardial wall stress and ventricular dysfunction, is commonly elevated in both MINOCA and MI-CAD cohorts compared to

healthy controls.⁶⁷ However, studies have not consistently demonstrated significant differences in NT-proBNP levels between these groups, limiting its discriminatory or prognostic value in MINOCA.⁶⁷ The precise role of natriuretic peptides in the pathophysiology or risk stratification of MINOCA remains largely unexplored.

Metabolic Biomarkers

Metabolic abnormalities, including hyperuricemia, hyperglycemia, and dyslipidemia, are associated with poorer prognosis in MINOCA patients.^{74,75,76} Elevated lipoprotein(a) (Lp(a)) is independently linked with increased cardiovascular risk, potentially through mechanisms involving microvascular dysfunction and promotion of systemic inflammation, evidenced by concomitant increases in CRP and IL-6.^{65,77,78} However, therapeutic strategies targeting these metabolic derangements have yet to be validated in this context, necessitating further investigation.

Vasoactive and Thrombotic Mediators

Vasoactive peptides such as endothelin-1 (ET-1) and neuropeptide Y (NPY), potent regulators of coronary vasomotion, are elevated in MINOCA patients with coronary microvascular dysfunction and epicardial vasospasm, underscoring their mechanistic relevance.^{79,80} Additionally, elevated plasma levels of soluble CD40 ligand (sCD40L), often accompanied by high CRP, implicate thrombo-inflammatory processes, particularly in MI subtypes involving plaque disruption or erosion.⁸¹

MicroRNAs (miRNAs)

Emerging evidence identifies circulating microRNAs (miRNAs) as promising biomarkers that may reflect specific pathophysiological mechanisms in MINOCA. Differential expression of miRNAs such as miR-16 and miR-26a (upregulated) and miR-1 and miR-133 (downregulated) correlates with coronary microvascular spasm, while miR-145 and miR-222 are linked to epicardial vasospasm.⁸² Other candidates, including miR-155-5p, miR-483-5p, and miR-451a, show potential as early markers of plaque rupture.⁸³ Despite their promise, these miRNAs remain

investigational and are not validated for routine MINOCA diagnosis, prognostic assessment, or treatment selection.

Although MINOCA and MI-CAD share overlapping acute-phase biomarker profiles, differences in inflammatory response resolution, metabolic derangements, and vasoactive mediator levels highlight distinct underlying pathophysiological pathways. To date, no specific, validated biomarker panel exists for unequivocal diagnosis or prognosis of MINOCA. Further well-designed studies are imperative to elucidate whether biomarker-driven strategies can refine etiological classification and enable personalized therapeutic approaches in this heterogeneous syndrome.

Noninvasive Imaging Evaluation

ECG

ECG is a fundamental diagnostic tool in patients presenting with acute MI. MINOCA patients can be classified as having STEMI or NSTEMI; however, the majority (approximately 70% to 80%) present as NSTEMI.¹ In non-atherosclerotic causes of MINOCA, such as epicardial coronary vasospasm, the ECG may show dynamic ST-segment elevation.¹ MINOCA mimickers, such as Takotsubo syndrome, can also cause ECG changes, most commonly ST-segment elevation, T-wave inversion, QT prolongation, or left bundle-branch block.^{84,85} These changes are often widespread and may not localize to a specific coronary territory. Given its accessibility and diagnostic value, ECG remains an essential first-line investigation in the evaluation of suspected MINOCA.

Echocardiogram

Echocardiography, like ECG, is a first-line imaging modality for assessing patients presenting with acute MI to assess LVEF and regional wall motion abnormalities.¹² According to the universal definition of MI, echocardiography can provide evidence of myocardial ischemia and is useful in diagnosing MINOCA.¹² When an embolic cause of MINOCA is suspected, echocardiography is essential to identify potential sources of embolism, such as intracardiac thrombi, valvular abnormalities, or a pat-

ent foramen ovale or atrial septal defect. In cases with multiple microinfarctions, transesophageal echocardiography (TEE) or a bubble contrast study can be particularly valuable for detecting cardiac shunts or other embolic sources.

Echocardiography is also valuable in identifying potential MINOCA mimickers. In Takotsubo syndrome, echocardiography is highly specific for identifying characteristic wall motion abnormalities, most commonly apical ballooning with basal hyperkinesis, although mid-ventricular or basal variants can also occur.⁸⁴ Additionally, echocardiography provides prognostic information in MINOCA, as studies have shown that a lower LVEF is associated with worse clinical outcomes.^{7,8}

Strain imaging

Myocardial strain imaging, assessed by echocardiography or CMR, quantifies myocardial deformation as the relative change in length. Global longitudinal strain (GLS), reflecting subendocardial longitudinal fiber function, is particularly sensitive to ischemic injury, as the subendocardium is the most vulnerable myocardial layer.⁸⁶

In MINOCA, strain imaging can detect subtle regional dysfunction even when LVEF is preserved.⁸⁶ This is clinically important as many MINOCA patients present with preserved LVEF, and GLS provides incremental diagnostic information beyond conventional echocardiography. A reduced GLS despite preserved LVEF should raise suspicion for ischemic myocardial damage and prompt further evaluation for underlying atherosclerotic or non-atherosclerotic causes. Strain imaging can also help differentiate MINOCA from mimickers, such as Takotsubo syndrome, which typically shows marked regional strain abnormalities with apical dysfunction in the classic phenotype, although other variants may demonstrate different patterns, while myocarditis often exhibits patchy or non-territorial strain reduction.⁸⁶

Strain imaging also has prognostic implications in MINOCA. GLS has been shown to predict adverse cardiovascular outcomes in ACS.⁸⁷ In patients with NSTEMI and LVEF >35%, both mechanical dispersion and GLS independent predictors of ventricular

arrhythmias, whereas LVEF itself was not, highlighting the added prognostic value of strain imaging.⁸⁷ A study in MINOCA patients using strain assessed by CMR demonstrated that lower GLS and left atrial reservoir strains independently predict MACE risk.⁸⁸ These findings support the role of strain imaging not only in diagnosis but also in risk stratification of MINOCA patients.

Coronary Computed Tomography Angiography (CCTA)

CCTA is a non-invasive technique used to assess coronary anatomy, myocardial bridging, and coronary stenosis.⁸⁹ Current guidelines recommend CCTA as an alternative to invasive coronary angiography to rule out ACS in patients with a low-to-intermediate likelihood of CAD.⁹⁰ In MINOCA, CCTA can detect features of plaque disruption or SCAD, although its accuracy and resolution is lower than invasive angiography, especially in distal vessels.^{18,89} CCTA is also valuable for longitudinal follow-up in SCAD, reducing the risk of dissection extension associated with repeated invasive angiography.¹⁸ Patients with SCAD frequently present with coronary tortuosity and myocardial bridging, both of which can be visualized by CCTA. Importantly, the ongoing MINOCA-GR study is evaluating the role of CCTA in characterizing atherosclerotic plaque burden, high-risk features, and pericoronary fat attenuation, aiming to refine diagnostic and prognostic assessment in this population.⁹¹ However, CCTA is limited by exposure to ionizing radiation and the potential adverse effects of iodinated contrast agents.⁸⁹

Cardiac Magnetic Resonance (CMR)

Given that multiple conditions can mimic MINOCA, current guidelines recommend performing CMR in all patients initially diagnosed with MINOCA.^{1,90} CMR provides high diagnostic accuracy by characterizing myocardial tissue, localizing injury, and distinguishing ischemic from non-ischemic causes. Late gadolinium enhancement (LGE) enables assessment of possible necrosis, alternative diagnoses, infarct size and distribution. In true MI, LGE typically presents in a subendocardial or transmural pattern. How-

ever, some patients with confirmed MI may exhibit absent LGE, potentially due to small infarct size, limited spatial resolution, or transient vascular occlusion.⁹² Additionally, regional myocardial edema detectable by T2-weighted imaging can serve as an early marker of injury.⁹² Importantly, there is no clear troponin threshold below which an abnormal CMR is unlikely among MINOCA patients.²¹

CMR is particularly valuable in identifying MINOCA mimickers. Myocarditis, present in approximately one-third of patients initially diagnosed with MINOCA, is characterized by non-ischemic LGE with matching edema.^{93,94,95} Previous meta-analyses have shown that male sex, younger age, and angiographically normal coronaries are independent predictors of CMR-confirmed myocarditis.⁹³ Recognizing myocarditis is important, as its treatment is generally supportive and does not require ischemic secondary prevention such as antiplatelet or statin therapy.¹

Takotsubo syndrome is another important differential diagnosis. CMR reveals characteristic wall motion abnormalities that may mimic left anterior descending artery or left main lesion, but lack the ischemic LGE distribution.^{84,96} Diagnosis is clinically relevant, as Takotsubo syndrome and cardiomyopathies in suspected MINOCA patients are associated with higher mortality. In a 3.5-year follow-up, overall all-cause mortality was 5.7%, with the highest mortality in the cardiomyopathy group (15%) compared to the MI (4%), myocarditis (2%), and normal CMR findings (2%).⁹⁷

CMR can also guide accurate diagnosis in patients with obstructive CAD. In an NSTEMI cohort with angiographically identified infarct-related arteries (IRAs), CMR reclassified the diagnosis in 12.5% of cases, most often to myocarditis, and identified a different infarct-related arteries in 14%, with some cases ultimately meeting MINOCA criteria.⁹⁸ Another study found that CMR changed the diagnosis in 54% and management in 41% of MINOCA patients.⁹⁹ More recently, a prospective multicenter study of 320 patients with suspected MINOCA demonstrated that CMR was associated with changes in clinical diagnosis and/or management in 63% of patients, including deprescription of

DAPT in 38% of patients initially prescribed DAPT.¹⁰⁰ The timing of CMR significantly affects diagnostic yield.⁹⁹ Early imaging, performed within 7 to 14 days post-MI, maximizes detection of myocardial injury before acute changes resolve, reducing the rate of inconclusive scans from 43% when performed after 2 weeks to 16% when performed within 2 weeks. This is particularly important for reversible conditions such as myocarditis and Takotsubo syndrome.⁹⁹ A large prospective study demonstrated that higher peak troponin levels and shorter intervals between MI onset and CMR independently increased the likelihood of a definitive diagnosis.¹⁰¹ Patients with peak troponin T ≥ 211 ng/L scanned within 14 days achieved a 94% diagnostic yield, compared with 53% when troponin was <211 ng/L and imaging was delayed beyond 14 days.¹⁰¹ Even in the lowest troponin decile (15-38 ng/L), the diagnostic yield remained 62%. No troponin threshold reliably excludes the utility of CMR, supporting its routine use in all suspected MINOCA patients.¹⁰¹ Furthermore, a study of MINOCA patients who underwent early CMR within 7 days showed that both %LGE and T2 mapping values were independent predictors of MACE at 3 years.¹⁰² Overall, variations in CMR diagnostic yield across studies may reflect differences in imaging timing, peak troponin concentrations, and patient selection. In summary, early routine CMR is a cornerstone in MINOCA evaluation, enhancing diagnostic accuracy, guiding targeted therapy, and improving prognostic assessment. However, although CMR is strongly recommended by international guidelines and its use is improving in recent years, often it is still limited by local availability and expertise.¹⁰³

Advanced imaging enhances diagnostic yield; however, most studies have been conducted in highly selected patients at specialized centers, raising concerns of selection bias. Availability and operator expertise vary widely, limiting external validity. Over-diagnosis is also possible, particularly in CMD and vasospasm, when comparator populations without myocardial injury are not included. In addition, differences in the timing of imaging may significantly influence diagnostic outcomes.

Invasive Imaging evaluation

Coronary angiography

Coronary angiography is fundamental in diagnosing MINOCA, as it confirms the absence of significant obstructive CAD, a key diagnostic criterion. However, coronary angiography has limitations, as plaque rupture or plaque erosion may not always be visible, and subtle lesions can be overlooked.^{1,21} Intravascular imaging modalities, including IVUS and OCT, have shown that atherosclerotic plaque disruption is more prevalent in MINOCA than angiography suggests.²¹ Previous studies using IVUS or OCT have identified plaque rupture or erosion in 29 to 38% of MINOCA patients.²² Notably, one study that excluded myocarditis by CMR prior to OCT reported plaque rupture in up to 80% of cases.⁴⁸ These wide variations in reported prevalence reflect methodological differences and selection bias. Together, the findings highlight the limitations of angiography and emphasize the crucial role of intravascular imaging in identifying the underlying mechanisms of MINOCA.

Intravascular Ultrasound (IVUS)

IVUS has greater tissue penetration (6-10 mm) compared to OCT (1-2 mm), allowing visualization of deeper vessel wall structures and assessment of calcium burden and plaque remodeling patterns. It is useful for evaluating dissections and ostial lesions.¹⁰⁴ However, its lower axial resolution (100-200 μ m) relative to OCT (10-20 μ m) limits its ability to detect microstructural features such as thin-cap fibroatheromas, small thrombi, or subtle intimal disruption.¹⁰⁴ A previous study using IVUS reported plaque disruption in approximately one-third of MINOCA patients.²² While IVUS can detect plaque rupture, its lower spatial resolution limits the ability to identify plaque erosion, a common atherosclerotic cause of MINOCA.^{1,27}

Optical Coherence Tomography (OCT)

OCT provides substantially higher spatial resolution than IVUS, enabling detailed characterization of plaque morphology and other coronary pathologies. With an axial resolution of 10-20 μ m and trans-

verse resolution of 20-40 μ m, OCT can differentiate tissue characteristics (fibrous, lipid-rich, or calcified plaques), detect unstable plaques, and distinguish between plaque rupture and erosion.¹⁰⁴ OCT is particularly useful for detecting plaque erosion, which is typically invisible to IVUS.¹⁰⁴ Studies combining CMR and OCT have shown complementary diagnostic value, achieving diagnostic yields of up to 85%, higher than either modality alone.²¹

Clinical data indicate that OCT-identified culprit lesions correlate with older age, diabetes, and angiographic abnormalities, but not with peak troponin levels or vessel stenosis severity.²¹ However, the identification of plaque disruption does not necessarily establish it as the cause of the acute MI and should be interpreted in the context of clinical presentation, ECG findings, and complementary imaging results. Notably, 34% of women with an OCT-identified culprit lesion had normal angiography, compared to 69% without a culprit lesion, emphasizing the incremental value of OCT in MINOCA evaluation.²¹ In vasospastic angina, OCT performed at the spasm site demonstrated plaque rupture in 12.5% and plaque erosion in 25% of cases, supporting a multifactorial pathophysiology in MINOCA.¹⁰⁵ OCT can also characterize SCAD, including visualization of true and false lumens.¹⁸ Overall, OCT is preferred over IVUS in MINOCA due to its superior spatial resolution, enhanced ability to characterize plaque morphology, and greater sensitivity for detecting subtle lesions such as plaque erosion, thrombi, and dissections that may be missed by IVUS.

Fractional Flow Reserve (FFR), Coronary Flow Reserve (CFR), and Index of Microvascular Resistance IMR

Fractional flow reserve (FFR) is an invasive index used to assess the physiological significance of coronary artery lesions. It is defined as the ratio of mean distal coronary pressure to mean aortic pressure during maximal hyperemia. An FFR value ≤ 0.80 is generally accepted as the threshold for functionally significant CAD. However, evidence supporting the role of FFR in MINOCA remained limited.¹

Previous studies have demonstrated that a greater angiographic atherosclerotic burden correlates with poorer outcomes.¹⁰⁶ Although data specifically evaluating FFR in MINOCA are limited, evidence from stable CAD populations suggests that up to 25% of patients with 30-50% stenosis have functionally significant lesions when assessed by FFR.¹⁰⁷ Therefore, FFR may be considered in selected MINOCA patients with borderline obstructive lesions to identify ischemia-causing stenoses that may not be evident on angiography alone. The 2019 AHA scientific statement proposed that, when FFR is performed, only patients with FFR values >0.80 should be included under the working diagnosis of MINOCA.¹ However, FFR findings should be interpreted cautiously during acute MI, as microvascular dysfunction may affect physiological measurements.

Despite its potential utility, the application of FFR in MINOCA is limited by procedural complexity, the need for hyperemic agents, increased cost, and prolonged procedural time. Coronary CT-derived FFR has emerged as a non-invasive alternative, providing both anatomic and physiological assessment with diagnostic performance comparable to invasive FFR.¹⁰⁸

CFR is another invasive physiological index, defined as the ratio of maximal hyperemic to resting coronary blood flow. Unlike FFR, CFR reflects the combined effects of both epicardial stenosis and microvascular function.^{40,109} A CFR <2.0 is generally considered abnormal and is associated with adverse outcomes in various patient groups, including MI patients.^{40,110} In MINOCA, a reduced CFR in the absence of epicardial stenosis suggests CMD as a potential underlying mechanism.

The IMR is a pressure- and thermodilution-derived invasive parameter that specifically quantifies microvascular resistance during maximal hyperemia, independent of epicardial artery status.^{40,109} An IMR ≥ 25 units is considered abnormal and indicative of CMD.⁴⁰ Compared with CFR, IMR is less influenced by hemodynamic variations, making it a more reproducible measure of microvascular function.¹¹¹ In MINOCA, an elevated IMR may be consistent with CMD; however, abnormalities in CFR or

IMR measured during or soon after acute MI may reflect myocardial injury, edema, microvascular obstruction, or preexisting microvascular dysfunction rather than the primary mechanism of the ischemic event. Therefore, microvascular testing is generally selective and may be deferred until after the acute phase. In contrast, the role of microvascular testing among stable outpatients with chronic stable angina (ANOCA/INOCA) is more clearly defined and endorsed by guideline documents.^{112,113,114}

In addition to these microvascular indices, provocative testing for coronary vasospasm has gained increasing importance in recent years. Coronary vasospasm represents a frequent cause of MINOCA.³ A definitive diagnosis generally requires provocative testing, as spontaneous vasospasm during angiography is uncommon.^{115,116,117} The 2023 ESC guidelines endorse intracoronary acetylcholine testing in patients with acute MI and suspected vasospasm.¹ Although earlier reports raised concerns regarding safety due to fatal complications with intravenous ergonovine,¹¹⁸ contemporary intracoronary protocols using short-acting agents such as acetylcholine, performed under strict monitoring in the catheterization laboratory, have proven to be safe.^{116,119} The incidence of serious complications is comparable to that of spontaneous vasospasm or diagnostic angiography, with most adverse reactions limited to transient brady- or tachyarrhythmias, occurring in 5-9% of cases.^{119,120,121}

Recent data underscore the prognostic implications of vasospasm testing. In a prospective study of 80 MINOCA patients, intracoronary acetylcholine testing within 48 hours of admission was positive in 46.2% without major complications; however, test positivity was associated with a significantly worse long-term prognosis, including higher rates of recurrent ACS and cardiac mortality at 36 months.¹²¹ Overall, provocative testing for vasospasm now has an established safety profile and diagnostic yield that justify its use as part of the interventional cardiologist's routine toolkit, particularly in MINOCA, with the potential to integrate microcirculatory assessment in selected cases.^{122,123}

Management

The management of MINOCA remains challenging due to its heterogeneous etiologies and the lack of randomized trials dedicated to this population. For patients with acute MI, secondary prevention therapies, including antiplatelets, statins, as well as, ACEI/ARBs, and possibly beta-blockers, particularly in patients with reduced LVEF, are essential to improve cardiovascular outcomes.¹¹⁵ However, since MINOCA patients generally have a lower atherosclerotic burden compared to those with MI-CAD, clinical management is often less aggressive.¹²⁴ Data from the SWEDEHEART registry showed that nearly half of patients who experienced recurrent MI after an initial MINOCA event had obstructive CAD at the time of the second event.¹²⁵ Mortality at 38 months was similar between patients with recurrent MINOCA and those with recurrent MI due to obstructive CAD, suggesting comparable long-term risk profiles.¹²⁵ Despite this, observational data from the ACTION-GWTG and SWEDEHEART registries indicated that patients with MINOCA are less frequently prescribed secondary prevention therapies such as aspirin, P2Y₁₂ inhibitors, statins, ACEI/ARBs, and beta-blockers compared to patients with MI-CAD.^{57,126}

An analysis of 9,466 MINOCA patients from the SWEDEHEART registry, with a mean follow-up of 4.1 years, showed that statins and ACEI/ARB use were associated with significant reductions in MACE, defined as all-cause mortality, MI, stroke, and heart failure.⁷ Beta-blockers showed a trend toward lower all-cause mortality, though not statistically significant. DAPT did not show clear benefit in this cohort.⁷ However, the observational design and lack of stratification by underlying MINOCA mechanisms limit causal interpretation of these findings. The CURRENT OASIS 7 trial included a post-hoc analysis of a MINOCA subgroup (6.7% of the total cohort) comparing high versus low doses of clopidogrel and aspirin.¹²⁷ In MINOCA patients, higher-dose clopidogrel (600 mg on day 1, followed by 150 mg daily on days 2-7, then 75 mg/day) was associated with worse outcomes compared to the standard dose (300 mg on day 1, then 75 mg/day), with

a composite endpoint of cardiovascular death, MI, or stroke occurring in 2.1% versus 0.6% at 30 days.¹²⁷ These findings emphasize the need for cautious use of intensified antiplatelet therapy in MINOCA and highlight the importance of tailoring treatment based on underlying pathophysiology.

For MINOCA patients with plaque disruption, secondary prevention should follow protocols similar to those for MI-CAD, including antiplatelet therapy and statins, as supported by evidence from the SWEDEHEART registry.⁷ The addition of a second antiplatelet agent may be reasonable in patients with confirmed plaque disruption, although its clinical benefit remains uncertain, as prior studies of DAPT in MINOCA populations did not consistently stratify patients by the underlying etiology.

For epicardial coronary spasm, calcium channel blockers (CCBs) are the cornerstone therapy, with non-dihydropyridine agents preferred initially. Combination therapy with dihydropyridines may be considered for persistent symptoms.^{1,29} The EDIT-CMD randomized trial in patients with ANOCA demonstrated that diltiazem significantly increased the transition from epicardial spasm to microvascular or no spasm compared with placebo. However, the primary endpoint was not met, and these findings may not be directly applicable to patients with acute MINOCA.¹²⁸ Short-acting nitrates are first-line for acute symptom relief, whereas long-acting nitrates are generally reserved for refractory cases due to the risk of tolerance.^{1,29} In patients with concomitant myocardial bridging and coronary spasm, CCBs can reduce contractility, and surgical unroofing may be considered if symptoms persist despite optimal medical therapy.²⁹

The management of CMD remains limited, as antianginal vasodilators are generally less effective on the microvasculature than on epicardial vessels. Most studies have excluded acute MI patients, and clinical trials specifically addressing CMD in MINOCA are lacking.⁴⁰ Symptom improvement has been reported with beta-blockers, CCBs, and, to a lesser extent, nitrates.^{1,40} A randomized study of 151 patients with anginal symptoms but no obstructive CAD demonstrated that tailored medical therapy

based on CMD and provocative testing improved angina and quality of life, although it did not reduce MACE at 6 months.¹¹⁴

The evidence of management in SCAD remains limited and is largely based on expert consensus. The use of anticoagulation and DAPT is controversial due to bleeding risks and the potential for hematoma propagation, despite the prothrombotic risk associated with intimal tears.¹⁸ While antiplatelet therapy generally follows standard ACS guidelines, the duration of DAPT in conservatively managed SCAD varies and remains uncertain, with some experts recommending up to one year, whereas others limit DAPT to 1-3 months.¹⁸ Beta-blockers should be considered for patients with reduced LVEF, arrhythmias, or hypertension and may reduce the risk of recurrence.¹⁸ Notably, a prospective observational study of 327 SCAD patients over a median follow-up of 3.1 years showed that beta-blocker use was associated with a 64% reduction in recurrent SCAD risk, although randomized evidence confirming this benefit is lacking.¹²⁹

Based on current evidence, treatment generally includes antiplatelet therapy and statins unless advanced imaging definitively excludes atherosclerosis.¹⁷ ACEI/ARBs are recommended in patients with decreased EF and based on observational data

ican Heart Association scientific statement further emphasized the importance of tailoring MINOCA treatment to the underlying mechanism.¹³⁰ Mechanism-specific pharmacological strategies for MINOCA are summarized in Table 2.

The majority of available results are derived from observational registries and post-hoc analyses of heterogeneous populations. Studies on therapeutic strategies in MINOCA are limited by this heterogeneity, and both selection bias and confounding further reduce the reliability of observed treatment effects. Moreover, randomized evidence is lacking, underscoring the need for mechanism-specific clinical trials. Importantly, MI therapies should not be overgeneralized to all MINOCA cases; treatment must be tailored to the underlying mechanism.

The PROMISE trial, the first randomized study of a stratified, mechanism-guided diagnostic and therapeutic approach in MINOCA, highlighted the impact of individualized management.¹³¹ In this multicenter study open-label trial, 101 patients with suspected MINOCA were randomized, of whom 92 had confirmed MINOCA and were included in the final analysis. Participants were randomized to stratified care involving a comprehensive diagnostic workup using OCT, intracoronary acetylcholine testing, cardiac MRI, and transesophageal echocar

TABLE 2. Risk Factors Associated With Different Mechanisms of MINOCA

CAUSE OF MINOCA	RISK FACTORS
Cause of MINOCA	Risk factors
Atherosclerosis	Traditional cardiovascular risk factors (age, hypertension, diabetes, dyslipidemia, smoking, family history)
Epicardial spasm	Age, smoking, inflammation (elevated high-sensitivity C-reactive protein), remnant lipoproteins, dyslipidemia, hypertension, hyperglycemia
Microvascular dysfunction	Age, sedentary lifestyle, smoking, dyslipidemia, hypertension, diabetes, obesity, family history
Spontaneous coronary artery dissection	Fibromuscular dysplasia, inherited arteriopathy, connective tissue disease, pregnancy, multiparity, exogenous hormone use, systemic inflammatory disease, migraine
Coronary embolism	Atrial fibrillation, hypercoagulable states, valvular heart disease, left atrial or left ventricular thrombus, infective endocarditis, cardiac tumors, cardiomyopathy

demonstrating reduced MACE.⁷ Beta-blockers are considered, particularly in patients with evidence of MI on CMR, reduced LVEF, or SCAD.^{1,90} CCBs are indicated for coronary vasospasm.¹ A recent Amer-

diography to identify the underlying mechanism, or to standard post-MI care without advanced testing. A specific mechanism was identified in 80% of patients in the stratified arm, and the initial clinical

diagnosis changed in more than 75%, underscoring frequent misclassification with routine care. The stratified approach significantly improved angina-related quality of life, with a 9.38-point greater improvement in the Seattle Angina Questionnaire Summary Score at 1 year compared with standard care ($P < 0.001$). Although rates of major adverse cardiovascular events were numerically lower (2.2% vs 8.5%), the difference was not statistically significant ($P = 0.18$).¹³¹ The study demonstrated that a comprehensive mechanism-guided diagnostic and therapeutic strategy improved angina-related patient-reported outcomes, supporting the use of an etiology-guided management strategy in MINOCA. However, the trial evaluated a combined diagnostic-and-treatment strategy rather than the independent clinical efficacy of individual diagnostic modalities. Moreover, its modest sample size, open-label design, and early termination limited its statistical power for hard clinical endpoints, including mortality and recurrent MI. Larger studies with longer follow-up are needed to confirm these findings. Current and ongoing large observational studies and randomized clinical trials evaluating treatment strategies in MINOCA are summarized in Table 3.

The MINOCA-BAT trial, designed to evaluate the efficacy of beta-blockers and ACEI/ARBs in patients with MINOCA and LVEF $\geq 40\%$, was prematurely terminated due to slow recruitment after enrolling only 192 of the planned 3,500 patients.^{132,133} A subsequent post-hoc analysis reported low cardiovascular event rates at 1 year, with no significant differences in residual symptoms or health-related quality of life between the randomized treatment groups.¹³³ However, the limited sample size and low event rates preclude definitive conclusions regarding the effectiveness of routine beta-blocker and ACEI/ARB therapy in this population.

For nonpharmacologic treatment, comprehensive cardiac rehabilitation is recommended for all patients with ACS.¹¹⁵ Cardiac rehabilitation consistently reduces cardiovascular hospitalizations, recurrent MI, cardiovascular mortality, and, in some studies, all-cause mortality.¹¹⁵ In MINOCA, a single-center prospective randomized trial of 524

patients demonstrated that exercise-based cardiac rehabilitation was associated with lower all-cause mortality and MACE over three years. However, the relatively small sample size, participant attrition, and potential selection bias warrant cautious interpretation of these findings.¹³⁴

Current challenges

The diagnosis and management of MINOCA remain challenging due to its heterogeneous etiologies and overlapping clinical presentations with MINOCA mimickers. Although advanced imaging modalities, such as CMR and intracoronary imaging, improve diagnostic accuracy, their use is often limited by availability, institutional protocol variability, and cost considerations, contributing to underdiagnosis or misclassification. Furthermore, a significant proportion of MINOCA patients do not undergo comprehensive evaluations to determine the underlying mechanism, resulting in suboptimal therapeutic strategies. In practice, CMR is recommended in most patients to exclude mimickers and characterize myocardial injury, while further investigations such as intracoronary imaging, vasospasm provocation, or thrombophilia testing should be individualized based on the clinical context, angiographic findings, and pre-test probability. A comprehensive diagnostic approach for MINOCA must consider cost, feasibility, and variability in healthcare resources. Current evidence on cost-effectiveness in MINOCA management remains limited. A retrospective study showed that CMR increases early costs modestly but becomes cost-neutral by 7 years and cost-saving by 10 years, largely by improving etiologic classification and reducing unnecessary exposure to DAPT.¹³⁵ Provocative spasm testing is diagnostically informative and safe in experienced centers, though implementation depends on local expertise.³⁴ Future studies are needed to determine risk-stratification tools to identify patients at highest risk who

TABLE 3. Summary of current and ongoing large observational studies and randomized clinical trials evaluating treatment strategies in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA)

STUDY	DESIGN	NUMBER OF	KEY BASELINE POPULATION/ INCLUSION	TREATMENT ARMS	MAIN OUTCOMES	REF
Lindahl B (2017) (SWEDEHEART)		9,136 survivors (>30 days) from 9,466 MINOCA admissions	MINOCA; mean age 65.3 years; 61% women; mean follow-up 4.1 years	Treatment at discharge vs no treatment: statins, ACEI/ARB, beta-blockers, DAPT	Statins and ACEI/ARBs were associated with lower MACE (HR 0.77 and 0.82 respectively). Trend for benefit with beta-blockers; no benefit with DAPT.	[7]
Bossard (2021) (CURRENT OASIS 7 subanalysis)	Post-hoc subanalysis of CURRENT-OASIS 7 randomized trial	23,783 MI patients with 1,599 (6.7%) with MINOCA	MINOCA patients enrolled in OASIS 7; mean age 57.6 years; 53% female; 30-day follow-up	Standard-dose clopidogrel DAPT (300 mg loading, then 75 mg daily) vs double-dose clopidogrel DAPT (600 mg loading, then 150 mg daily days 2–7, then 75 mg daily)	Composite 30-day outcome (CV death, MI, or stroke) occurred in 2.1% on double-dose vs 0.6% on standard dose (HR 3.57, 95% CI 1.31–9.76). No significant difference in obstructive CAD subgroup.	[127]
Montone (2026) (PROMISE)	Multicenter randomized, open-label	92 patients	MINOCA (STEMI and NSTEMI) excluding Takotsubo syndrome and myocarditis; follow-up 1 year	Stratified care (systematic diagnostic work-up (OCT, ACh testing, TEE, and cardiac MRI) diagnostics + cause-specific pharmacologic therapy) vs standard care (routine workup + standard ACS therapy)	Primary: Improvement in angina (SAQSS) at 1 year: +9.38 points in stratified care vs standard care (P<0.001). Secondary: MACE at 1 year: 2.2% in stratified care vs 8.5% in standard care (p=0.186).	[131]
Ongoing trials						
MINOCA-GR (NCT04186676)	Prospective, multicenter observational registry	60 patients	MINOCA (STEMI and NSTEMI) excluding Takotsubo syndrome and myocarditis; follow-up 1 year	Imaging-based (CCTA at baseline and 6 months)	Primary: atherosclerosis extent/severity, high-risk plaque features, pericoronary fat attenuation, angina burden (SAQ) Secondary: MACE, Health status, rehospitalization	[91]
Montone (2022) (PROMISE)	Multicenter randomized, open-label	180 patients	MINOCA (STEMI and NSTEMI) excluding Takotsubo syndrome and myocarditis; follow-up 1 year	Precision approach (tailored diagnostics + cause-specific pharmacologic therapy) vs standard approach (routine workup + standard ACS therapy)	Primary: improvement in angina (SAQSS) at 1 year. Secondary: MACE at 1 year, cost analysis.	[136]

STUDY	DESIGN	NUMBER OF	KEY BASELINE POPULATION/ INCLUSION	TREATMENT ARMS	MAIN OUTCOMES	REF
StratMed-MINOCA (NCT05198791)	Randomized, open-label	350 patients	MINOCA with coronary microvascular dysfunction (IMR ≥ 25); follow-up 6 months	Eplerenone (starting 25 mg, uptitrated to 50 mg after 2 weeks) vs standard of care	Primary: change in NT-proBNP. Secondary: health-related quality of life, myocardial blood flow at 6 months.	NCT05198791
Terminated trial						
Nordenskjöld (2021) (MINOCA-BAT)	Multicenter randomized, open-label 2×2 factorial	3,500 patients	MINOCA discharged without clinical HF and LVEF $\geq 40\%$; mean follow-up 4 years	Randomize to beta-blocker vs no beta-blocker and ACEI/ARB vs no ACEI/ARB	Primary: composite MACE (all-cause death, readmission for MI, ischemic stroke, HF). Trial terminated due to low inclusion rate.	[132]

ACS acute coronary syndrome; ACEI angiotensin-converting enzyme inhibitor; ACh Acetylcholine; ARB angiotensin II receptor blocker; CAD coronary artery disease; CCTA coronary computed tomography angiography; CI confidence interval; CV cardiovascular; DAPT dual antiplatelet therapy; HF heart failure; HR hazard ratio; HRQoL health-related quality of life; IMR index of microvascular resistance; LVEF left ventricular ejection fraction; MACE major adverse cardiovascular events; MI myocardial infarction; MINOCA myocardial infarction with non-obstructive coronary arteries; MRI Magnetic Resonance Imaging; NSTEMI non-ST-segment elevation myocardial infarction; NT-proBNP N-terminal pro-B-type natriuretic peptide; OCT Optical Coherence Tomography; SAQSS Seattle Angina Questionnaire Summary Score; STEMI ST-segment elevation myocardial infarction; TEE transesophageal echocardiogram.

would benefit from more advanced investigation, especially in resource-limited settings. Evidence-based treatment approaches for MINOCA are still limited. As a result, current treatment strategies are largely extrapolated from studies in MI-CAD populations or observational registries, which may be confounded and may not fully address the diverse pathophysiological mechanisms underlying MINOCA.

Future direction

Advancement in the understanding and management of MINOCA requires large multicenter randomized clinical trials that evaluate therapeutic strategies tailored to specific MINOCA subgroups based on etiology. There is ongoing debate among experts as to whether confirmed myocardial infarction without obstructive CAD should continue to be categorized as 'MINOCA' or simply as MI, given the current $\geq 50\%$ stenosis threshold. The role of emerging biomarkers such as microRNAs and the utility of physiologic coronary assessments in MINOCA remain limited, and further studies are needed to clarify their diagnostic and prognostic value. The development and validation of standardized diagnostic pathways, integrating early CMR, intracoronary imaging, and coronary physiological assessments, are essential to improve diagnostic yield and promote mechanism-directed management, while also assessing cost-effectiveness. The application of machine learning and artificial intelligence to multimodal datasets, including imaging results, biomarker profiles, and clinical parameters, may facilitate more precise risk stratification, identify patients most likely to benefit from advanced diagnostic testing, and guide mechanism-specific treatment strategies while maintaining cost-effectiveness.

Conclusion

MINOCA represents a heterogeneous subset of acute MI, encompassing a wide spectrum of etiologies ranging from atherosclerotic plaque disruption

to non-atherosclerotic mechanisms. Despite the absence of obstructive CAD, MINOCA is associated with significant morbidity and mortality, highlighting the importance of early recognition and thorough evaluation. Advanced imaging modalities, including early CMR and intracoronary imaging, have significantly improved diagnostic accuracy, allowing for better differentiation between ischemic and non-ischemic causes. Therapeutic strategies remain largely extrapolated from MI-CAD populations and observational evidence, which may not fully address the diverse pathophysiological processes underlying MINOCA. Statins, ACEI/ARBs, and antiplatelet therapy remain the cornerstone of secondary prevention in patients with evidence of atherosclerotic involvement, while management of non-atherosclerotic causes requires a tailored, mechanism-specific approach. Recent randomized data have demonstrated that a mechanism-guided diagnostic and therapeutic strategy improves anginal symptoms and quality of life at 1 year compared with standard post-MI care without advanced testing. Future efforts should focus on large-scale randomized trials to define evidence-based treatments for distinct MINOCA subtypes, validate standardized diagnostic algorithms, and assess long-term clinical outcomes with extended follow-up.

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