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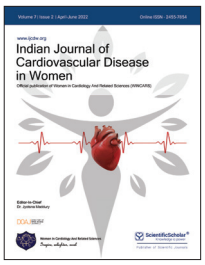

Review Article *Cardiovascular*

MINOCA: Predictors and Future Management

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ABSTRACT

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA), identified by clinical documentation of an acute MI without significant coronary artery obstruction (stenosis <50%) on coronary angiography, is an evolving area of cardiovascular medicine. MINOCA poses a substantial challenge as there remains uncertainty in valid clinical diagnostic criteria and treatment strategies. Unfortunately, those with this condition experience high rates of mortality, re-hospitalization, worse quality of life, and poor prognosis. Effective management currently aims at identifying the underlying mechanism of the infarction, which can be caused by a variety of factors. This review will discuss the latest in pathophysiology, diagnostic techniques, management and future research of patients with MINOCA.

Keywords: MINOCA, Predictors, Mortality

INTRODUCTION

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA), identified by clinical documentation of an acute MI (AMI) without significant coronary artery obstruction (stenosis <50%) on coronary angiography, is an evolving area of cardiovascular medicine. Studies have suggested that MINOCA has a favorable long-term prognosis compared to MI-coronary artery disease (CAD). However, one study showed that MINOCA has lower cardiovascular mortality in comparison, but comparable rates of ischemic stroke, reinfarction, and all-cause mortality in a 20-year follow-up period.[1] In a 2023 study, patients with MINOCA who presented with STEMI were noted to have a 40% higher risk of 5-year all-cause mortality than those with STEMI in the setting of obstructive disease.[2] Due to this, there is growing recognition of this patient population in research impacting clinical practice, patient outcomes, and future management. MINOCA poses a substantial challenge as there remains uncertainty in valid clinical diagnostic criteria and treatment strategies. The prevalence is estimated to range between 5% and 10% among MI patients. In contrast to prior beliefs that these patients with MINOCA or INOCA had a benign prognosis, more recent data suggest otherwise. Studies indicate that the presence of non-obstructive CAD is associated with a higher risk of major adverse cardiovascular events (MACE) compared to those with normal coronary arteries.[3] Unfortunately, those with this condition experience high rates of mortality, rehospitalization, worse quality of life, and poor prognosis.[4] Effective management currently aims at identifying the underlying mechanism of the infarction, which can be caused by a variety of factors including plaque rupture, erosion, microvascular dysfunction, and coronary vasospasm.[5] This review will discuss the latest in

pathophysiology, diagnostic techniques, management, and future research of patients with MINOCA.

INCIDENCE AND PREVALENCE

Worldwide the incidence and prevalence of MINOCA as a percentage of all MIs has some variability dependent on differing study inclusion criteria and populations. An analysis combining data from 23 studies that looked at 806,751 AMIs revealed a MINOCA prevalence rate of 8.1%.[6] Various national databases across the globe, including those within the United States, Japan, Poland, and Sweden have documented rates between 2.7% and 10%.[6] Another large systematic review examining 28 publications determined an approximate 6% prevalence.[7]

The condition disproportionately impacts certain patient demographics. Compared with patients who had MI, those with MINOCA were younger with a median age of 61 years, more likely to be female, but less likely to have dyslipidemia.[6] Almost half of MINOCA patients are women, whereas only 25% of AMI sufferers have typical obstructive CAD.[8] Black and Hispanic patients are more likely to experience MINOCA.[6]

The occurrence of MINOCA is similar in locations around the world, indicating its universal presence, although the true rate may be underestimated due to difficulty in confirming a diagnosis. According to common consensus, the genuine incidence and prevalence rate is between 5% and 10%. This statistical metric is critical for healthcare organizations and resource distribution, as well as alerting healthcare clinicians about this large population of AMl patients.

PATHOPHYSIOLOGY

The pathophysiology of MINOCA appears to be complex and is not fully understood, comprising numerous mechanisms that ultimately result in myocardial ischemia and cardiac-myocyte injury without effective obstruction of epicardial coronary arteries. Key aspects encompassing the pathophysiological mechanisms of MINOCA are listed in Table 1.

Inflammation is the principal pathologic component contributing to MINOCA, inducing endothelial dysfunction, platelet activation, and increased thrombotic potential. These pathophysiologic mechanisms in combination ultimately culminate in MINOCA. Both coronary thrombus formation and plaque disruption are common findings in MINOCA, which is demonstrated by optical coherence tomography (OCT). Disruptions like these result in triggered inflammatory response which exacerbates myocardial injury.[9] Coronary artery vasospasms, one of the MINOCA mechanisms, are also associated with inflammation and endothelial dysfunction.[10]

Table 1: MINOCA pathophysiologic mechanisms.

Plaque disruption	• Atherosclerotic plaque destabilization including rupture, erosion, and calcified nodules • Does not result in significant luminal stenosis
Spontaneous coronary artery dissection	• Formation of a false lumen within the wall of epicardial coronary artery
Coronary artery vasospasm	• Hyper-reactivity of vascular smooth muscle within epicardial or microvascular vessels • Vasoconstriction is inducible on provocative testing (acetylcholine or ergonovine) through angiography
Coronary microvascular dysfunction (impairment of myocardial perfusion at the microvascular level)	• Microvascular spasm • Coronary slow flow phenomenon • Microvascular thrombosis
Coronary embolism	• Dependent on origin—direct (LA, LV, valvular), paradoxical, or iatrogenic (intracoronary or valvular intervention)

*The complexity of multiple intersecting mechanisms can complicate diagnosis and treatment of myocardial infarction with non-obstructive coronary disease (MINOCA). These multiple underlying causes, either independent or overlapping, should be considered when deciding the treatment plan

Compared to those who suffer from "traditional" obstructive MI, these patients often have a different risk profile. A significant study, VIRGO, showed that females have 5 times higher odds of having MINOCA.[11] In addition, these patients tend to be younger in age and have fewer traditional cardiovascular risk factors. In the setting of not-fully-understood pathophysiologic mechanisms and unique risk factor profiles and populations, the diagnosis is challenging. Advanced diagnostic techniques such as intravascular imaging and cardiac magnetic resonance imaging are often necessary to elucidate the specific underlying causes in individual cases.[12]

DIAGNOSIS

MINOCA is diagnosed according to the Fourth Universal Definition of MI, to include the absence of angiographic obstructive CAD, with no lesion >50% in any major epicardial vessel. The diagnosis should exclude other causes that can result in troponin elevation such as pulmonary embolism and sepsis, in addition to exclusion of non-ischemic causes for myocyte injury such as myocarditis.[8]

During coronary angiography differences in the degree of irregularity and plaque burden can be obtained. All patients

should have <50% stenosis as defined, but categorization can occur, differentiating between those with 30% and 50% moderate coronary atherosclerosis and those with <30%. Distinguishing between these categories ensures that patient's with truly non-obstructive CAD are classified as MINOCA.[11,13]

Fractional flow reserve (FFR) can be a useful diagnostic measure; a preserved FFR of >0.80 typically indicates the absence of flow-limiting stenosis. More advanced OCT or intravascular ultrasound (IVUS) can also be considered refer to [Table 2], with OCT being the newer intravascular imaging method using infrared light instead of ultrasound,[14] providing more detailed insight of coronary artery abnormalities that may not be evident on standard angiography.[15] It is an intracoronary imaging technique that provides high-resolution images of the coronary walls, allowing for identification of plaque erosion or rupture and coronary artery dissection.[16] However, it has limitations in its ability to directly assess a lesion's hemodynamic significance. FFR, with the ability to assess functional significance of stenosis, does not provide morphological information of the plaque itself.[17] While both are valuable diagnostic modalities, they are not without their strengths and limitations. In cases where IVUS or OCT is inconclusive, there has been an emerging role in high-sensitivity cardiac techniques, including cardiac MRI. This is now the gold standard for non-invasive cardiac assessment accuracy, safety, and consistency.[14]

Coronary vasospasm is another identified etiology contributing to MINOCA. The primary method used to diagnose spasm involves administering doses of acetylcholine directly into the coronary arteries and assessing the response through contrast angiography, with >90% narrowing of a coronary artery considered diagnostic.

MANAGEMENT

The management of MINOCA remains a complex challenge due to its heterogeneous nature and lack of standardized guidelines. Based on limited evidence with no prospective and randomized controlled trials, management is largely tailored to individual mechanisms of MINOCA that are currently recognized [Table 3].[18,19] The cornerstone of MINOCA management is undergoing a comprehensive diagnostic evaluation to identify the underlying cause, including intravascular imaging, cardiac MRI, and other specialized tests. Once the etiology is determined, treatment can be tailored accordingly.[11]

Table 2: Review of diagnostic modalities for myocardial infarction with non-obstructive coronary disease.

Fractional flow reserve	Assess hemodynamic significance of lesions in the coronary arteries; can also evaluate coronary microvascular dysfunction
Optical coherence tomography	Identify plaque disruption, thrombosis or spontaneous coronary artery dissection
Cardiac magnetic resonance imaging	Emerging gold standard; Differentiates between ischemic and non-ischemic causes such as takotsubo or myocarditis

MINOCA caused by plaque disruption typically follows standard AMI protocols, including dual antiplatelet therapy (typically of shorter duration), statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In cases of coronary vasospasm, calcium channel blockers remain the cornerstone of treatment, often supplemented with long-acting nitrates.

Beta-blockers are generally avoided in this case due to their potential to exacerbate vasospasm.[12] Patients with coronary microvascular dysfunction may be prescribed beta blockers and calcium channel blockers along with medications that enhance endothelial function such as ACE inhibitors or ARBs.

Current management approaches primarily rely on the consensus of experts and observations from studies like the SWEDEHEART registry[20] which have hinted at benefits of using statins and ACE inhibitors or ARBs for MINOCA patients. Nevertheless, the ongoing MINOCA BAT trial is anticipated to offer conclusive evidence regarding the effectiveness of beta-blockers and ACE inhibitors or ARBs for this population.[21] The treatment of MINOCA should be customized for each patient by considering factors such as the etiology, individual patient characteristics, and clinical judgment. It is important to check in and reevaluate because a patient's situation can evolve over time.

Regardless of the cause behind the condition and its different pathophysiology when compared to CAD-MI, it is advisable for all patients experiencing MINOCA to follow secondary prevention strategies such as modifying risk factors and participating in cardiac rehabilitation programs. The components of cardiac rehabilitation, including a structured exercise training program, risk factor management, and psychosocial support groups, is likely beneficial for both groups with its emphasis on secondary prevention. One study by He *et al*. investigated the effect of cardiac rehab on patients with MINOCA, as studies are lacking. This prospective cohort study included 524 MINOCA patients, and found that long-term exercise cardiac rehab improved physical health as measured by the Short-Form 36 survey with a reduction in all-cause mortality in a 3-year follow-up period.[22]

THE FUTURE

Current evidence on MINOCA has brought attention to its intricate nature and the importance of individualized

Table 3: Treatment approaches for each MINOCA mechanism

Mechanism	Medication recommendations	Contraindications	Duration of therapy
Coronary vasospasm	• Calcium channel blockers (verapamil, diltiazem) • Long acting nitrates (short term)	• Beta-blockers (can exacerbate vasospasm)	• Continue calcium channels for 6–12 months if recurrent episodes
Atherosclerotic plaque rupture	• (DAPT) Aspirin, P2Y12 • inhibitor (clopidogrel, ticagrelor), Statins	• Monitor for bleeding	• 6–12 months for dual antiplatelet therapy • Then continue aspirin for life
Microvascular Dysfunction	• ACE or ARB • Beta blockers, CBB • Statins • Nitrates	• Non-dihydropyridine calcium channel blockers	• Long-term for managing comorbidities
Spontaneous coronary artery dissection	• Aspirin • Beta blockers	• Anticoagulant	• Beta blockers and anti-platelet therapy for 6 months - 1 year
Coronary thromboembolism	• Anticoagulation on (Warfarin, DOACs)	• Thrombolytics, unless no contraindication	• Individualized treatment • Thrombectomy or anticoagulation therapy, often 3–6 months

DAPT: Dual antiplatelet therapy, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, CBB: Calcium channel blocker, DOACs: Direct oral anticoagulant, MINOCA: Myocardial infarction with non-obstructive coronary disease

treatment approaches for effective management. The future of research is tailored toward several key aspects such as enhanced diagnostic methods and crafting customized therapies based on specific underlying factors. Advanced imaging modalities such as OCT show promise in identifying the causes of MINOCA, and future studies may refine these methods to accurately distinguish between atherosclerotic and non-atherosclerotic mechanisms.[23] Novel biomarker research is also underway with promising intentions for clinicians in effectively making a diagnosis, uncovering underlying mechanisms, and aiding in treatment decisions.[24]

Developing prediction models particular to MINOCA patients utilizing comprehensive, prospective studies may help us better understand long-term prognosis and is crucial for optimizing management strategies in these patients. It is important to maintain awareness on gender-specific factors of the condition given the higher prevalence of MINOCA in women. Studies like the WARRIOR trial (Women's Ischemia Trial to Reduce Events in Non-obstructive CAD) were designed to provide critical data to inform guidelines on managing women with MINOCA, a population at elevated risk for MACE but underrepresented in clinical research. The WARRIOR trial is a multicenter, prospective, randomized, blinded, and outcome evaluation (PROBE design) aimed at assessing the efficacy of intensive medical therapy versus usual care in women with MINOCA.[25] Being that MINOCA is more prevalent among women, the results of this trial will provide important data that will aid in informing guidelines for managing this growing and challenging patient population, both underscoring the importance of gender-specific research and clarifying clinical practice decisions.

As our knowledge advances and continues to evolve, the focus will likely shift toward more precise, personalized approaches in both research and clinical care. Optimizing secondary prevention strategies specific to these patients is an important area of future research. The ongoing MINOCA-BAT trial, expected to complete in 2025, is examining conventional secondary prevention therapeutics (ACE/ARB and beta-blockers) in patients after a diagnosis of MINOCA has been made. This trial may influence future treatment guidelines for this diverse patient group, potentially improving outcomes through targeted interventions.[26] Ongoing and future research efforts will continue to be aimed at better understanding the complex pathophysiology of MINOCA, prognosis, and prognostic models, in addition to advancing more targeted and evidence-based management strategies.

CONCLUSION

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) poses a substantial challenge as there remains uncertainty in valid clinical diagnostic criteria and treatment strategies. Advanced imaging modalities such as optical coherence tomography (OCT) show promise in identifying the causes of MINOCA, and future studies may refine these methods to accurately distinguish between atherosclerotic and non-atherosclerotic mechanisms. The management of MINOCA remains a complex challenge due to its heterogeneous nature and lack of standardized guidelines. Currently, management is largely tailored to individual recognized mechanisms, which are reviewed in this article. Ongoing and future research efforts will

continue to be aimed at better understanding the complex pathophysiology of MINOCA, prognostic models, and advancing more evidence-based management strategies.

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