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Tackling MINOCA: A Comprehensive Review of its Mechanisms and Management

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Abstract: Patients with acute myocardial infarction (AMI) may show no blockage in their coronary arteries. This condition is known as myocardial infarction with non-obstructive coronary arteries (MINOCA). It affects between 6–8% of individuals with spontaneous MI who are referred for coronary angiography screening. The key mechanisms responsible are coronary artery spasm, thrombosis, and atherosclerosis. Identifying the underlying mechanism of infarction determines how MINOCA is managed. A systematic approach for the diagnosis is recommended. Diagnostic yield is achieved by combining cardiac magnetic resonance imaging, provocative testing for coronary spasm, multivessel intracoronary imaging, and invasive coronary angiography. Majority of the practice guidelines and treatment regimens are currently based on data from patients with MI with obstructive coronary artery disease (MI-CAD) and secondary prevention guidelines for atherosclerotic disease. The risk of long-term adverse outcomes remains high for MINOCA patients. Hence, in order to determine the best course of treatment for patients with MINOCA, more clinical trials are needed. This review emphasizes the pathophysiology of MINOCA, highlighting its various causes, challenges in diagnosis, the need for personalized treatment, and the necessity for further research on clinical outcomes.

Keywords: *MINOCA; Atherosclerosis; Coronary Arteries; Coronary Angiography; Cardiac Magnetic Resonance*

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I. INTRODUCTION

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is an important subtype of myocardial infarction (MI). The presentation of MI without any coronary artery disease (CAD) has been observed for decades, MINOCA was introduced in the year 2013 [1]. The European Society of Cardiology (ESC) states that MINOCA is diagnosed when an acute myocardial infarction (AMI) occurs according to the third universal definition of MI [1]. Additionally, The American Heart Association (AHA) scientific statement defines MINOCA as a condition that meets the criteria for acute MI, characterized by the absence of ≥50% obstruction in any of the major epicardial vessels as seen on a coronary angiography, and the presence of no other clinically apparent non-ischemic diagnoses such as sepsis, pulmonary embolism, Takotsubo syndrome, and myocarditis [2]. There are about 6-8% of individuals who are diagnosed with MI but have no significant blockages in their coronary arteries. Throughout the years, researchers have noted an increase in the incidence of MINOCA, as mentioned in a Spanish registry [3]. The pathophysiological mechanisms for MINOCA are primarily explained by coronary (epicardial vasospasm, coronary microvascular disease, spontaneous coronary artery dissection, coronary thrombus/embolism) and noncoronary (Takotsubo cardiomyopathy, myocarditis) diseases which can potentially mimic MI [4,5]. Historically, MINOCA has often been overlooked and misdiagnosed, but the results from a recent multicenter study suggest it requires more attention. Results of the study show that the course of MINOCA in patients with acute myocardial infarction was not benign; the functional and psychosocial results, as well as the 1- and 12-month mortality, were comparable to those of patients with myocardial infarction caused due to coronary artery disease. MINOCA was prevalent in 11% of the patients (mostly women) [6]. A systematic review performed over a small number of studies viewed the prognostic factor and exhibited that patients with MI and obstructive coronary arteries (MIOCA) have a 12-month all-cause death rate of about 6.7%, compared to 3.5% in patients with MINOCA [7]. It has become evident that MINOCA is a common condition, particularly among individuals who experience an early onset

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of MI. The diagnosis of MINOCA primarily relies on the presence of clinical acute MI. When obstructive coronary artery disease is ruled out in patients with acute myocardial infarction, more testing should be performed to determine the underlying cause of the ischemia and to initiate the appropriate therapy [7].

II. ETIOLOGIES AND PATHOPHYSIOLOGY OF MINOCA:

There are two types of pathophysiologic mechanisms for MINOCA: extra-cardiac and cardiac. The former is further split into atherosclerotic and non-atherosclerotic origins. Plaque disruption or erosion are common atherosclerotic mechanisms, whereas thromboembolism, epicardial coronary artery spasm (CAS), spontaneous coronary artery dissection (SCAD), coronary microvascular dysfunction (CMVD), and an imbalance between the myocardium's oxygen requirements and supply are examples of non-atherosclerotic mechanisms [8,9]. In addition to these underlying causes, there are diseases that mimic MI. Consequently, it is critical to identify MINOCA mimics, such as myocarditis, stress-induced cardiomyopathy, and non-ischemic cardiomyopathy [10,11]. All Etiologies, their prevalence, Mechanisms and Diagnostic tools are summarized in Table 1.

A. Plaque Disruption Without Full Blockage

Plaque disruption without full blockage is the main cause of MINOCA. A non-obstructive atherosclerotic plaque can tear or erode, creating a thrombus. This thrombus quickly breaks down, leaving little to no angiographic evidence of blockage. Studies show that 38 to 40 percent of MINOCA patients show signs of plaque disintegration [12]. This temporary blockage leads to infarction and myocardial ischemia. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) help spot plaque disruption. OCT can reveal plaque rupture as a break in the fibrous cap, exposing the lipid-rich core. Erosion involves thrombus formation on an intact plaque surface [13]. Using intracoronary imaging is crucial for accurate diagnosis.

B. Coronary Vasospasm

A sudden, intense narrowing of the epicardial coronary artery causes coronary vasospasm. The vasoconstriction causes the reduction of blood flow, causing transient myocardial ischemia, which mimics MI [14]. This is more often associated with endothelial dysfunction and is more prevalent in smokers and cocaine abusers. The diagnosis is through an invasive acetylcholine (Ach) provocation testing process (Ach administered in coronary arteries) where >90% vasoconstriction is observed. The CASPAR trial also reported positive acetylcholine tests in MINOCA patients. The mechanism involves vascular smooth muscle hyperactivity leading to the temporary occlusion of vessels that either spontaneously resolve or, with vasodilators, leave the blockage with no angiographic findings [11].

C. Microvascular Dysfunction

Coronary microvascular dysfunction (CMD) involves the impairment of the function of the small coronary vessels, which are less than 500 µm in size. These are not visible on the standard angiography, but it still leads to inadequate myocardial perfusion and ischemia [8]. CMD can also result from endothelial dysfunction. In endothelial dysfunction, the vessel lining cannot regulate the blood flow, or sometimes, due to microemboli, causing distal vessel obstruction. For example, emboli due to fungal endocarditis vegetations can predispose to formation of multiple microemboli which can subsequently cause microvascular dysfunction [15]. Metabolic syndrome is also associated with endothelial dysfunction leading to thrombosis and atherosclerotic plaque formation [16]. Stress cardiac magnetic resonance (CMR), which is non-invasive, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) are the diagnostic tools preferred. Reportedly, up to 50% of MINOCA patients have coronary microvascular dysfunction (CMD) [12]. WISE (Women's Ischemia Syndrome Evaluation) has reported that reduced CFR is seen in almost half of the women with non-obstructive CAD, which emphasizes the role of CMD in MINOCA [8].

D. Takotsubo Cardiomyopathy

Also called Stress cardiomyopathy, Takotsubo cardiomyopathy is triggered either by severe emotional or physical stress. Transient left ventricular dysfunction is characteristic of Takotsubo cardiomyopathy. This is most commonly seen in post menopausal women. While it mimics MI with very similar symptoms and ECG changes, it often lacks CAD (Obstructive Coronary disease), which mimics non-ischemic MINOCA. Diagnosis with CMR is essential as it reveals the characteristic wall motion abnormalities, such as apical ballooning without late gadolinium enhancement that is typical of infarction. The critical part of this diagnosis is to capture the changes in a timeline of two weeks [11].

E. Myocarditis

Myocarditis is an inflammatory process of the myocardium. The troponin elevation and its non-ischemic nature mimic MI-like symptoms. One-third of reported MINOCA cases are due to myocarditis, with the highest prevalence in men and younger patients [17]. The diagnosis of myocarditis requires ischemic causes. CMR is the gold standard; it detects myocardial edema and late gadolinium enhancement, which represent the inflammatory nature.

F. Supply-Demand Mismatch

Supply-demand mismatch is classified as a Type 2 MI. About 50% of the patients with type II AMI are categorized as MINOCA because they do not have severe obstructive coronary artery disease. This occurs when myocardial oxygen levels are lower than the demand levels, causing ischemia and myocardial injury without obstructive CAD [4]. Severe anemia, tachycardia, or hypotension can result in a supply-demand mismatch. Clinical Assessment and biomarkers are the key to identifying the underlying conditions, like arrhythmia or hypoxia, in this etiology [18,19].

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Table 1 Causes and Mechanisms of MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries)

Cause	Mechanism	Diagnostic Tools	Prevalence in MINOCA	Key Reference
Plaque Disruption	Plaque rupture/erosion with transient thrombus	Optical Coherence Tomography (OCT), Intravascular Ultrasound (IVUS)	38–40%	[8,12]
Coronary Vasospasm	Sudden epicardial artery constriction	Acetylcholine provocation	~27%	[11,17]
Microvascular Dysfunction	Impaired small vessel function (endothelial dysfunction, microemboli)	Coronary Flow Reserve (CFR), Index of Microcirculatory Resistance (IMR), Cardiac Magnetic Resonance (CMR)	Up to 50%	[8,18]
Takotsubo Cardiomyopathy	Stress-induced transient Left Ventricular (LV) dysfunction	CMR, echocardiography	~11%	[11]
Myocarditis	Myocardial inflammation	CMR	~33%	[8]
Supply–Demand Mismatch	Oxygen supply-demand imbalance	Clinical assessment, biomarkers	~50% of type 2 MI	[8,14]

III. CLINICAL PRESENTATION:

MINOCA is presented with symptoms indistinguishable from those of obstructive MI, which complicates the initial diagnosis. Patients experience acute chest pain, dyspnea, diaphoresis, or other acute coronary syndrome symptoms. Electrocardiographic changes such as ST elevation or depression, elevated biomarkers, especially troponins, confirm the diagnosis of myocardial injury, meeting the MI criteria [19]. All these findings can lead clinicians to a presumed diagnosis of an obstructive MI, until performing coronary angiography that reveals no significant blockages [11]. The similarities to obstructive MI point towards the need for further investigation to differentiate MINOCA from other myocardial injuries [2].

IV. DIAGNOSTIC WORKUP

MINOCA can be difficult to diagnose, and in up to 25% of cases, the underlying reason is still unknown despite thorough investigation [9]. It becomes essential to use a variety of cutting-edge diagnostic modalities, including non-invasive methods like CFR, cardiac computed tomography angiography (CCTA), and CMR, as well as intravascular studies (OCT, IVUS), and fractional flow reserve (FFR). A systematic and multi-step approach helps identify the correct etiology [9]. Following are the diagnostic steps involved in finding the root cause.

A. Coronary Angiography

Coronary angiography is the first-line imaging technique preferred for suspected acute MI, helpful for assessing the coronary arteries. In a MINOCA workup of more than 50% of the population, there is no stenosis of any major epicardial artery. Only MINOCA is to be considered as a working diagnosis [20]. Performing Coronary angiography helps rule out obstructive CAD as it provides information on the underlying mechanisms and allows for further evaluation as needed [11].

B. Optical Coherence Tomography (OCT) And Intravascular Ultrasound (IVUS)

Intravascular imaging with OCT and IUVS detects subtle plaque disruptions like ruptures, erosion or spontaneous coronary artery dissection (SCAD), which is usually missed on a standard angiography [11,21]. Performing OCT provides high-resolution images of the vessel wall, identifying the fibrous cap rupture or a thrombus on intact erosion. IVUS offers a much deeper analysis of the vessel wall. In 40%of the cases when OCT is performed, it helps in the diagnosis of MINOCA [13]

C. Cardiac Magnetic Resonance Imaging (CMR)

Cardiac magnetic resonance imaging (CMR) is a very helpful tool to differentiate ischemic from non-ischemic causes of myocardial injury and is considered the gold standard for MINOCA. While CMR reveals subendocardial or transmural late gadolinium enhancement (LGE) it is indicative of myocardial infarction; the epicardial or mid-myocardial LGE is indicative of myocardial edema and inflammation. If there are wall motion abnormalities in findings with minimal or no LGE, it is likely to be Takotsubo cardiomyopathy [20]. CMR helps in diagnosing 70-80% of MINOCA cases [2].

D. Provocative Testing for Coronary Spasm

By administering Acetylcholine or ergonovine during angiography, coronary vasospasm can be induced to confirm it as the cause of MINOCA. This method is especially useful in patients with recurring chest pain or patients who are at a higher risk due to factors like smoking and drug abuse (eg: cocaine). If vasoconstriction greater than 90% is observed, it confirms vasospasm and is observed in almost 30% of MINOCA cases [11,17].

E. Functional Assessment of Microvascular Function

Invasive tests like CFR, IMR, or non-invasive tests like Positron Emission Tomography scan (PET) or stress CMR provide necessary assessment on coronary microvascular dysfunction, which is found in 50% of MINOCA cases [5]. Often the findings include abnormal myocardial blood flow,

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indicating microvascular issues which are related to endothelial dysfunction or microemboli [11,18].

F. Transthoracic Echocardiography (TTE)

TTE is a useful tool in the assessment of left ventricular function and wall motion abnormalities that can be found in Takotsubo syndrome or other cardiomyopathies [17,20].

V. MANAGEMENT:

MINOCA represents a heterogeneous clinical conundrum. Specific guidelines for the diagnostic criteria of MINOCA exist which are provided by the ESC. But tailored therapeutic regimens and specific pharmaceutical approaches are still under exploration, while the ESC also recommends treating MINOCA of unknown cause according to secondary prevention guidelines for atherosclerotic disease [1]. It is essential to determine the underlying cause and etiology, in order to deliver an early and appropriate specialized targeted therapy. As a result, a systematic approach to diagnosis is recommended.

In cases with patients of MINOCA who are attributed to plaque disruption, the treatment recommended to them includes an initial period of DAPT (dual antiplatelet therapy) which is followed by monotherapy to be taken lifelong, alongside high-intensity statins, to be taken in individuals even with a minimal plaque burden as well as beta-blockers and ARBs or ACE inhibitors. According to the AHA, antiplatelet treatment and statins should be used for MINOCA patients with plaque disruption [22]. Based on three observational studies conducted, it is indicated that treatment with ARBs and ACE inhibitors has some amount of beneficial effects on the outcome of such patients [23,24]. Symptomatic antianginal treatment with beta-blockers, calcium channel blockers or long-acting nitrates is often needed. If the underlying mechanism is identified as vasospasm then the usage of calcium channel blockers is the most effective symptomatic therapy. A cohort study conducted on patients with SCAD (Spontaneous Coronary Artery Dissection) has shown a decline in probability of recurrences in survivors of SCAD who were on beta-blockers [25]. The pharmacological therapy for SCAD remains arguable and uncertain with no specific clinical trials to date supporting a definitive therapy suggestion for MINOCA patients. Paradoxically, Beta blockers might aggravate occurrence of microvascular or epicardial spasm that might benefit a coronary vasoconstriction by unmasking alpha adrenoreceptors in the coronary circulation. The SWEDEHEART trial was unsuccessful in showing a proper significant statistical approach in treatment benefit with beta-blockers in a 1-year span amongst MINOCA patients. It also states that a noticeably lower incidence of adverse events was observed when statins and ACEI/ARB were used.

The MINOCA-BAT is an ongoing trial investigating and exploring definitive preventive treatments for MINOCA patients, specifically ACE inhibitors. [22,26]. The data on usage of calcium channel blockers remain finite and minimal with no proper conclusive evidence of showing long-term MACE (Major adverse cardiovascular event) reduction in patients [27,28]. The dual antiplatelet treatment (DAPT) may be considered during the acute phase of SCAD and for up to 1-year in patients who did not undergo any percutaneous coronary intervention (PCI) [29]. Additionally, aspirin may be effective in preventing the formation of any thrombotic complications in patients who have fibromuscular dysplasia; in contrast, it must be avoided in patients who are at risk of bleeding. Based on various small randomized controlled trials conducted, the efficacy of non-traditional antianginal treatments, such as those with L-arginine, has also been highlighted [30]. An elevation in inflammatory parameters or D-dimer levels might otherwise suggest a different angle like pulmonary embolism (PE) or myocarditis.

Performing dilatation with the help of balloon cutting (with or without stenting) can be a viable option to enlarge the true vessel lumen and fenestrate the intramural haematoma [31]. In case of any longer/deep MBs (Myocardial Bridging) identified as being responsible for MINOCA, especially if it needs more than one stent, then surgical options like supra-arterial myotomy (unroofing) or coronary artery bypass grafting (CABG) should be considered. The evidence comparing surgical management by performing CABG to that of myotomy is still limited, so a proper recommendation could not be provided [32]. A study performed with over 72 patients with Takotsubo syndrome indicates that such patients benefit from a combination therapy that includes anti-thrombotic and heart failure therapy for a period of 2 months after the acute event has occurred. Additionally lifestyle modifications can be done including few steps like a healthy diet, exercise, weight management, cessation of smoking and management of stressful activities [33], and by mitigation of modifiable cardiovascular risk factors which include blood pressure control, diabetes control and lipid lowering therapy, are measures that can aid and are essential to optimize long term outcomes in individuals. A study has shown that with CR (Cardiac Rehabilitation) of about 20min-30min exercising on a treadmill or by performing bicycle exercise, three times a week, was effective in improving the overall well-being and mortality outcomes of patients who presented with MINOCA [34].

VI. PROGNOSIS:

A. Beyond Coronary Angiographic Normalcy

Normal coronary angiographies are found more frequently in younger MINOCA patients. A study by Bainey et al. revealed in-hospital death rates were similar among patients with normal coronary angiographies and those with stenosed arteries. Though prognosis varies with etiology, risk of MI and death was found to be similar in patients regardless of type, with 10% approximate 5-year mortality risk [35].

B. Short-Term, Long-Term Outcomes and Recurrence Rates

MINOCA patients had comparatively higher 1-year mortality risks vs Non S-T Elevation Myocardial Infarction (NSTEMI) and CAD patients in a retrospective analysis of patients from the ACUITY study. The VIRGO study revealed similar 12-month prognoses for MINOCA and MI-CAD in those aged <55 years [36]. A study by Zeng et al. found no

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significant difference in major adverse cardiovascular events (MACE), including cardiac death, stroke, or MI recurrence, between atherosclerotic or non-atherosclerotic MINOCA [37]. However, 12-month mortality was found to be lower in MINOCA patients compared to MI and CAD according to the Beltrame group, highlighting data on MINOCA prognosis contrast significantly [36]. The SWEDEHEART registry revealed a 14% mortality rate in MINOCA patients after a 4-year follow-up [36]. Another study revealed that all-cause 2-year death and MI recurrence did not differ significantly between MINOCA and MI-CAD patients [38]. The VIRGO study found similar or worse long-term prognosis among patients with MINOCA and ST-Elevation Acute Coronary Syndrome (STE-ACS) [36].

C. Factors Associated with Worse Prognosis

Hyperglycemia due to metabolic syndrome, or inflammatory and neurohormonal responses that lead to elevated SHR (Stress Hyperglycemia Ratio), both contribute to increased risks of MACE. A study by Amhadi et al. found atherosclerotic plaque types to be related to mortality rates. The highest incidence of 9.6% was seen among non-calcified plaques, followed by 3.3% in mixed plaques and 1.4% in calcified plaques [39]. Additionally, a study by Andishmand et al. revealed that LVEF (Left Ventricular Ejection Fraction) reduction post-MI independently increased the incidence of sudden cardiac death. [40]

VII. FUTURE DIRECTIONS AND RESEARCH GAPS

A. Implementing Phenotype-Specific Management

Phenotype specific management of MINOCA may prove advantageous owing to its multifactorial pathophysiology [41,42]. In the CURRENT-OASIS 7 trial, it was revealed that dose intensification did not appear to have an additional benefit over the standard clopidogrel-based DAPT therapy, but instead implied possible harm. Furthermore, the PURSUIT trial found that though obstructive CAD patients benefited from eptifibatide, MINOCA patients did not. In both trials, no change in bleeding events was noted in MINOCA patients [43].

B. Advancements in Diagnostic Modalities

Due to the limitations of coronary angiography in non-obstructive plaque identification, imaging modalities like CT, IVUS, OCT, and CMR are being increasingly employed for risk stratification and accurate diagnosis [39].

Intracoronary vascular imaging by IVUS and OCT is beneficial in evaluating inapparent coronary angiographic lesions. By integrating both ultrasound-based and infrared light-based technologies, an improvement in the characterization of atherosclerotic plaque by hybrid IVUS-OCT imaging is achieved [43]

The use of CCTA (Coronary Computed Tomography Angiography) as an alternative to ICA (Invasive Coronary Angiography) is beneficial in estimating the extent of coronary stenosis. In addition to identifying obstructive and non-obstructive lesions, CCTA can also differentiate plaques based on calcification and risk. A study with 3393 patients initially done by Chan et al. [44], which was later discussed by Edpuganti et al. [45] using the AI-Risk Model showed strong MACE and cardiac death predictability with CCTA regardless of coronary atherosclerosis. With a 74% diagnostic yield observed with CMR alone, using AI in CMR can amplify sparse Signal-to-Noise Ratio (SNR) in LGE and also detect infarcted and MVO (Microvascular Obstruction) regions accurately by utilising DL-based algorithms.

C. Limitations in Current Literature

Presently, MINOCA treatment strategies are mainly devised from studies of obstructive CAD patients or observational studies. MINOCA-BAT is the first clinical trial evaluating ACE/ARB and placebo therapy for MACE in a case-control setting; however, the study is yet to be completed, thereby emphasizing the lack of adequate randomized control trials (RCTs) in assessing MINOCA pharmacotherapy. Imaging modalities like FFR must also be studied further in terms of use and reliability in MINOCA [9,42,43].

VIII. CONCLUSION:

MINOCA is a clinical entity that is becoming increasingly acknowledged for being linked to a higher risk of MACE in individuals who present with AMI. Systematic approaches to diagnosis are advised because the management of MINOCA varies depending on the underlying mechanism of infarction. The highest diagnostic yield is obtained by combining CMRI, invasive coronary angiography, multivessel intracoronary imaging, and provocative testing for coronary spasm. Women are disproportionately afflicted by MINOCA, due to physiological and societal aspects. Future studies must focus on developing a multimodal diagnostic technique for the accurate identification and diagnosis of MINOCA. As well as the implementation of focused evidence-based treatment to prevent MACE and increase survival. Overall, managing MINOCA is a major clinical issue due to its complex nature, the need for a variety of diagnostic techniques, and the uncertain therapy approaches.

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- *Consent to Participate:*

Not applicable.

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  T.J. conceptualized the study, designed the structure, coordinated the literature review process, and edited the full manuscript.

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