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Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): A Review of the Current Position

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Abstract
Myocardial infarction with nonobstructive coronary arteries (MINOCA) remains a puzzling clinical entity that is characterized by clinical evidence of myocardial infarction (MI) with normal or near-normal coronary arteries on angiography (stenosis <50%). Major advances in understanding this condition have been made in recent years. The precise pathogenesis is poorly understood and is being studied and examined further. Guidelines indicate that MINOCA is a group of heterogeneous diseases with different mechanisms of pathology. Since there are multiple possible pathological mechanisms, it is not certain that the classical secondary prevention and treatment strategy for MI with obstructive coronary artery disease (MI-CAD) is optimal for MINOCA patients. The prognosis and predictors for MINOCA patients remain unclear. Although the prognosis is slightly better for MINOCA patients than for MI-CAD patients, MINOCA isn't always benign. The aim of this paper was to review the literature and evaluate MINOCA epidemiology, clinical features, etiology, diagnosis, treatment, and prognosis.

Introduction

In the past 50 years, with the innovation and development of medical technology, the diagnosis, management, and prognosis of acute myocardial infarction (AMI) has been significantly improved, with modern technologies including electrocardiogram (ECG), cardiovascular (CV) disease intensive care, coronary angiography (CAG), reperfusion treatment, high-sensitivity cardiac troponin (hs-cTn) detection, etc., playing an important role. Early studies reported that 90% of AMI patients have an obvious coronary artery obstruction (a degree of stenosis >50%). In the remaining 10% of CAG patients, the degree of stenosis is <50%, and is termed nonobstructive coronary artery myocardial infarction (MINOCA). MINOCA is a distinct type of myocardial infarction (MI) that was first described long ago; in a 2016 ESC position paper, it was considered a "working diagnosis" analogous to heart failure, prompting further evaluation regarding its underlying mechanisms [1]. Several large-scale registration studies indicated the proportion of MINOCA in the MI population to be 1–15% [2–4]. MINOCA is a syndrome caused by various pathophysiologic mechanisms, and due to the absence of culprit artery and obstructive coronary artery disease (CAD), a char-

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acteristic finding on CAG in MINOCA, it is often misdiagnosed and not given full attention. According to recent reports, the incidence of major CV events (MACE) in MINOCA patients has increased in the past few years and the age of onset is younger, so MINOCA should be given more attention by clinicians. Currently, there is no recognized standard protocol for effective management of MINOCA, often meaning that the optimal time for treating nonobstructive CAD patients gets postponed. MINOCA has a different prognosis and etiology from obstructive CAD. It is imperative to distinguish an analysis of the potential causes and clinical characteristics of MINOCA and provide diverse treatment techniques for patients.

Definition and Diagnosis Criteria

In order to evaluate nonobstructive CAD in advance and determine the appropriate treatment, the ESC published a working position paper on MINOCA in April 2016 [1] which included a definition of the condition as well as its clinical features, etiology, and pathogenesis. MINOCA was specifically added as a type of MI in the Fourth Universal Definition of Myocardial Infarction (UDMI) published by the ESC in 2018 [5]. According to this publication, the diagnosis of MINOCA must meet 3 criteria. First, a definitive diagnosis of AMI must be made (the same as that of MI caused by obstructive CAD [MI-CAD]). Second, CAG must show nonobstructive coronary disease, i.e., no obstructive coronary disease (i.e., no coronary stenosis ≥50%) is found in any possible infarction-related angiography, including normal coronary arteries (no stenosis <30%) and mild coronary atherosclerosis (stenosis >30 and <50%). Third, there is no clinical finding of other specific diseases that cause AMI, e.g., myocarditis and pulmonary embolism. Cases complying with the above criteria can be diagnosed as MINOCA. This position paper provided a diagnostic basis for cardiologists in future clinical work. Cardiologists must also realize that "normal" CAG does not necessarily imply that there is no coronary heart disease. On the contrary, if the patient has symptoms or signs of myocardial ischemia such as chest pain, a further examination should be performed to find out whether the patient has nonobstructive CAD, as approximately normal or near-normal angiography cannot meet the needs of diagnosis and treatment.

Prevalence, Clinical Features, and Epidemiology

The recorded prevalence of MINOCA differs according to different approaches to understanding the definition of MINOCA and gathering information. Previous studies demonstrated that the prevalence of MINOCA in patients with AMI is 1–15%. In 322,523 AMI patients enrolled in the ACTION Registry-GWTG, the incidence of MINOCA was 5.9% [6]. In 8,305 patients presenting with MI in the ANZACS-QI program trials, 10.8% received a diagnosis of MINOCA [7]. A large clinical COAPT study investigating AMI patients reported that MINOCA was identified in 5.8% of the patients with MI [3]. The multicenter registry of MINOCA-TR reported an incidence of 6.7% in the Turkish population [8]. The GENESIS-PRAXY trials identified a prevalence of MINOCA of 8.2% in 1,210 young patients presenting with AMI [9]. According to the ORPKI Polish National Registry, the prevalence of MINOCA in STEMI and NSTEMI patients was found to be 7.8% [10]. The NZACS-QI registry reported 15% of MINOCA in patients admitted to hospital with AMI in the NZ population [11]. Recent research from the CMS and NCDR CathPCI Registry indicated that of 286,780 patients admitted with AMI, 16,849 (5.9%) were categorized as MINOCA patients [12]. Compared with patients with obstructive MI, i.e., MI-CAD, MINOCA patients are more likely to be young [2, 13] and tend to have less hyperlipidemia [2]. Notwithstanding the causes of MINOCA, ECG can represent ST-segment elevation (STE) or non-ST-segment elevation (NSTE). STE and NSTE have similar ratios in female patients [1, 2]. Recent studies on the relationship between MINOCA and personality traits have shown that there are no significant differences between MINOCA patients and patients with coronary heart disease on rating scales [14]. Anxiety and depression are also frequent in MINOCA patients relative to MI-CAD [15–17] and directly related to poor prognosis [16]. The seasonal variation of MINOCA and MI-CAD is different, and the incidence of MINOCA increases slightly in summer and autumn. MINOCA and MI-CAD are most common in the morning [18], and some studies have found that the onset time of MINOCA is not correlated with the prognosis of the disease [19].

Pathogenesis and Underlying Etiology of MINOCA

MINOCA is a complex clinical condition with a variety of causes including epicardial vascular causes, i.e., plaque rupture, coronary spasm, and spontaneous coro-

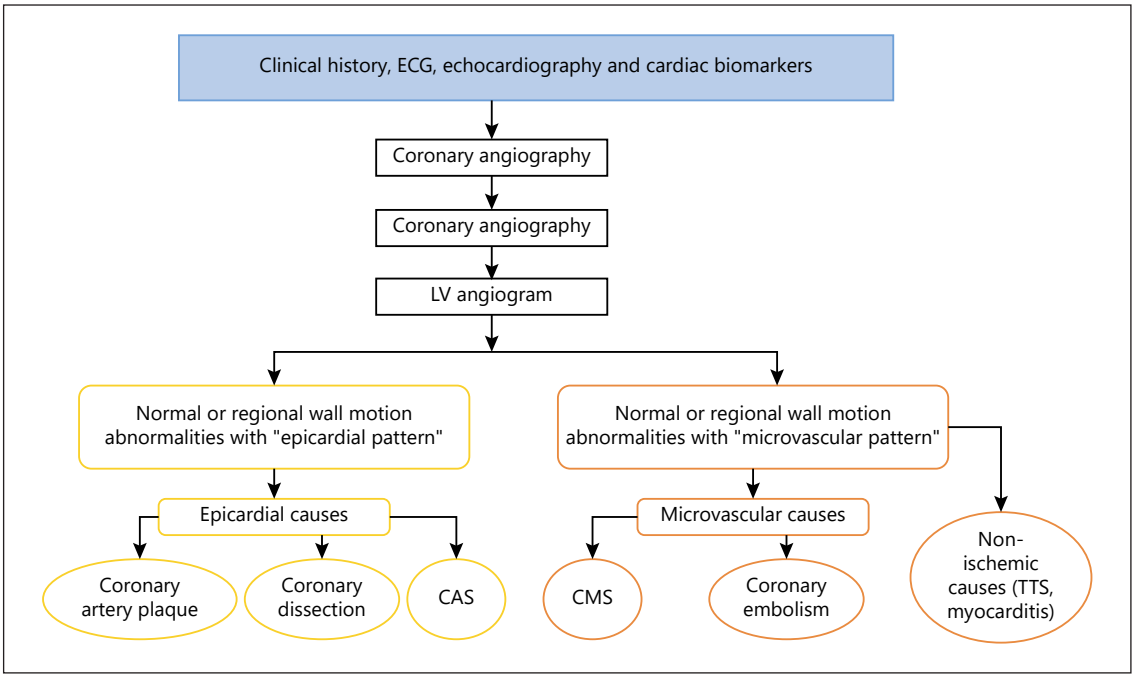

Fig. 1. Underlying causes and etiology of MINOCA. ECG, electrocardiogram; LV, left ventricular; CAS, coronary artery spasm; CMS, coronary microvascular spasm; TTS, Takotsubo syndrome.

nary dissection, and microvascular causes, i.e., coronary thromboembolism, coronary microvascular dysfunction, and microcirculation spasm (Fig. 1).

Epicardial Vascular Causes

Coronary Plaque Disruption

Coronary plaque disruption is one of the most common causes of MINOCA [20], and generally involves plaque rupture, ulcer, corrosion, erosion, and plaque bleeding. Approximately 40% of MINOCA is caused by plaque rupture [21]. Once the coronary artery plaque ruptures, the vascular endothelium is impaired, causing thrombosis and partial or complete obstruction of the coronary artery lumen, but the degree of stenosis of the coronary artery is <50%, which manifests as MINOCA [22]. In some studies, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) were used to analyze thin-cap fibroatheromas (TCFA) [23]. The results showed that with a coronary artery stenosis rate of 30–49%, 18% of a plaque was a vulnerable plaque, i.e., a high risk factor for CV events. Plaque rupture can only be diagnosed by intracoronary imaging (preferably with high-resolution OCT) or, to a lesser extent, by IVUS [1, 24]. Coronary computed tomographic angiography (CTA) does not provide enough details of the lumen interface.

Coronary Artery Spasm

Coronary artery spasm represents the strong response to endogenous or exogenous vasoconstrictors of the vascular smooth muscle, which is one of the main causes of epicardial artery spasm in MINOCA. It has been found that 16–74% of patients with MINOCA show induced spasm, suggesting that coronary artery spasm is a common and essential pathogenesis of MINOCA [25–27]. Patients with coronary artery spasm may have angina pectoris at night or in the early morning, accompanied by short STE. If there is no STE on ECG, an intracoronary stimulation test is needed to diagnose coronary artery spasm. Ergonovine or acetylcholine (ACh) is usually used to stimulate the spasm of the coronary artery [28]. If the blood vessel diameter is reduced by >75% and clinical symptoms or signs of myocardial ischemia are observed, coronary artery spasm can be diagnosed.

Spontaneous Coronary Dissection

Spontaneous coronary dissection refers to spontaneous tearing of the intima of the coronary artery under the condition of nonhuman factors, and hematoma formation when blood enters the middle or subintima of the coronary artery, which leads to sharp narrowing of the lumen and serious obstruction of the blood flow, mani-

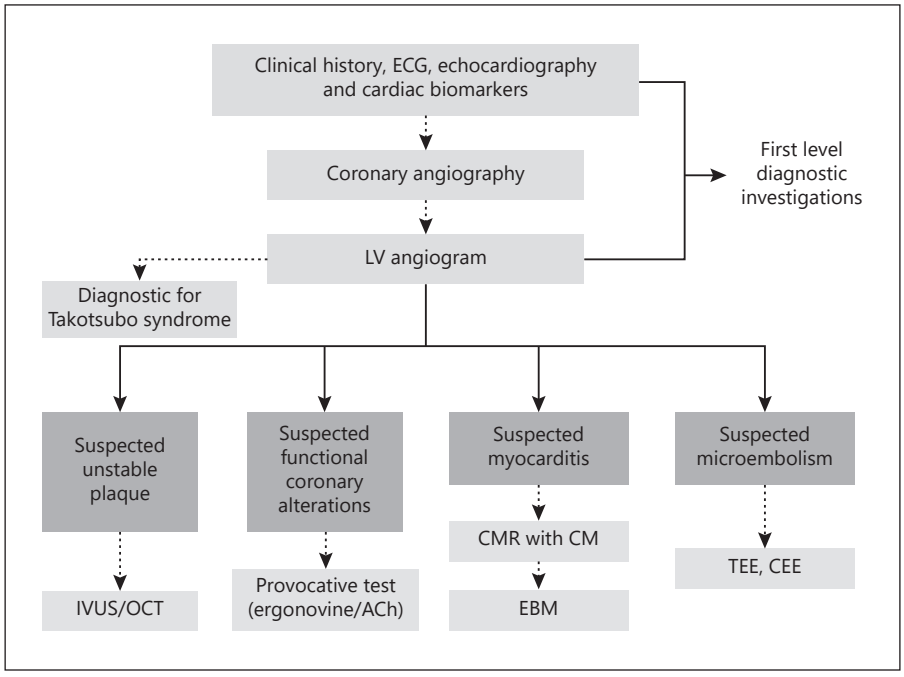

Fig. 2. Clinical assessment of MINOCA patients. ECG, electrocardiogram; LV, left ventricular; IVUS, intravascular ultrasound; OCT, optical coherence tomography; ACh, acetylcholine; CMR, cardiac magnetic resonance; CM, contrast medium; EMB, endomyocardial biopsy; TEE, transesophageal echocardiography; CEE, contrast-enhanced echocardiography.

festing as acute coronary syndrome (ACS). Spontaneous coronary dissection often occurs in young women [29]. Such patients do not have obstructive lesions on CAG and are diagnosed as MINOCA. At present, the diagnosis of spontaneous coronary dissection is made by means of CTA, IVUS, or OCT. IVUS and OCT are more accurate. OCT is less affected by calcification than IVUS and can show the changes in dissection length and lumen diameter more clearly, thereby guiding coronary intervention and prognostic evaluation [24].

Microvascular Causes

Coronary Microvascular Spasm

Transient transmural myocardial ischemia may occur during spontaneous or triggered angina pectoris, in which the ECG indicates a deviation in the ST segment, but the epicardial coronary artery is normal. If the coronary artery test for ACh stimulation is positive and there is a change in ischemic ECG, but no epicardial coronary spasm, then microvascular angina might be diagnosed. Previous studies have shown that there is evidence of microcirculatory spasm in about 16% of MINOCA patients [28]. Two studies showed that 43–54% of MINOCA patients experienced microcirculatory spasm [25, 26]. The above symptoms can be reproduced by the intracoronary ACh test, triggering ischemic ECG changes (0.1 lower in ST-segment in at least 2 leads) without epicardial spasm (a diameter reduction >90%).

Nonischemic Causes

Takotsubo Cardiomyopathy

The prevalence of Takotsubo cardiomyopathy (stress cardiomyopathy) in ACS is 1.2–2.2% [30]. Clinical manifestations are sudden poststernal pain accompanied by STE and/or T-wave inversion on ECG. The clinical process of Takotsubo cardiomyopathy is usually transient and reversible, and prone to occur in postmenopausal women with emotional or physical stress. Most patients have STE (44%) usually accompanied by elevated cTn (95%), but with a low peak value, i.e., not consistent with major ECG changes or left ventricular (LV) dysfunction [30]. Pathophysiological mechanisms of stress cardiomyopathy include plaque rupture, abnormal pressure reflex, catecholamine toxicity, spontaneous coronary thrombolysis, and acute microvascular spasm. The diagnosis mainly depends on echocardiography, ventriculography, and magnetic resonance imaging (MRI) [1].

Myocarditis

Earlier studies regarded myocarditis as the most common noncoronary cause of MINOCA; it was diagnosed according to basic symptoms and clinical manifestations, e.g., AMI. MINOCA is attributed to acute myocarditis in about one-third of patients [31]. Acute myocarditis is mainly caused by the Coxsackie virus, adenovirus, influenza virus, or EB virus. Patients with myocarditis may have clinical manifestations of chest pain, an elevation of

myocardial necrosis biomarkers, and ST-segment changes on ECG, but CAG findings often show no significant vascular stenosis. However, endothelial cell injury and microvascular dysfunction may be the result of myocarditis and/or PVB19 infection in vascular cases [32]. At present, an endomyocardial biopsy is still the "gold standard" for the diagnosis of acute myocarditis [33]. Cardiac MRI (CMR) has a great diagnostic value for viral myocarditis, which is mainly manifested as ACS [34].

In 2017, the ESC considered including MINOCA in the definition of MI and suggested that left ventriculography or echocardiography could be used to evaluate the motion of the LV wall [1]. The Fourth UDMI [5] redefined the concept of myocardial injury and states that the term MINOCA is only for patients presenting with clinical ischemia. It has been stated that Takotsubo syndrome and myocarditis do not belong to the working diagnosis of MINOCA. Nevertheless, given the dynamic nature of the concept, underlying mechanisms of the MINOCA could identify as one of these diseases; accordingly, and for uniformity, Takotsubo syndrome and myocarditis are included in a nonischemic category. However, it is still important to "re"-review alternative nonischemic causes when there is no definitive diagnosis.

Clinical Assessment of MINOCA

MINOCA is a group of syndromes involving ≥1 causes. The increased level of cTn in noncardiac diseases, such as pulmonary embolism and kidney damage, should be first excluded when we determine the main cause as a "working diagnosis." Cardiac causes, including diseases relevant to structural myocardial dysfunction and ischemic myocardial injury, should then be considered. Clinical history, myocardial enzymes, ECG, echocardiography, CAG, and LV angiography are the techniques used to provide an initial diagnosis which forms the basis for determining the cause of MINOCA. For patients with MI-CAD, the diagnosis is clear, and the treatment plan can be selected according to the CAG findings.

However, in patients with MINOCA, coronary athermanous plaque tends to develop eccentrically, so that CAG mostly shows normal or mild stenosis. With the aid of the following tests, we may further clarify the cause [24]. CMR is a fundamental tool for the diagnosis of MINOCA, which aids in understanding the potential causes of MINOCA but also provides a clear diagnosis of MI. CMR is of great importance when assessing microvascular disease [1, 24]. It can detect myocardial activity, tissue morphology, myocardial edema, and myocardial perfusion simultaneously as well as accurately assessing myocardial perfusion, coronary resistance, and diastolic filling under the endocardium and pericardium. In the advanced stage, late gadolinium enhancement (LGE) can provide evidence of myocarditis and endocardial myocardial infarction, of great value in the assessment of health management in MINOCA patients. Tornvall et al. [35] reported 556 cases of MINOCA and 115 cases of ischemic cardiomyopathy confirmed by CMR. While it is not clear whether nonvascular MINOCA is caused by plaque rupture or vasospasm, it can be excluded by referring to the LGE type, which provides the basis for the formulation of clinical treatment options. Leurent et al. [36] used CMR tools in continuous MINOCA patients and found that myocarditis accounted for 60%, AMI accounted for 16%, Takotsubo cardiomyopathy for 14%, and a normal performance accounted for 10%. IVUS, as an invasive intravascular imaging technology, is helpful for the early detection of progressive vascular remodeling, a preliminary diagnosis of rupture or erosion of the coronary plaque, and plaque stability assessment. Related studies [21] showed that IVUS determined plaque rupture or ulcers in 40% of female patients with MINOCA. In addition, transesophageal and/or contrast-enhanced echocardiography can be used to detect the source of cardiac embolism in coronary microvascular embolization. At present, OCT is more sensitive than IVUS and has a higher ruptured-plaque detection rate as well as compensating for IVUS limitations in detecting bleeding and plaque ulcers. Previous studies [37] have shown a specificity and sensitivity of OCT of 75 and 92%, respectively, in the identification of plaques with a large lipid pool and a thin fiber cap. In an acute setting, left ventriculography or echocardiography should be performed to determine wall motion, enabling clinicians to make a meaningful diagnosis of Takotsubo cardiomyopathy [1]. Coronary spasm provocation tests (invasive coronary ACh provocation tests) can be performed by hyperventilation, ACh stimulation, ergometrine stimulation, etc. The carrying out of coronary spasm stimulation tests and intervention therapy is equally important for the prognosis of patients [28]. A certain amount of ACh or ergometrine can be injected into the left and right coronary arteries for patients suspected of MINOCA, and the spasm of the coronary artery can be evaluated after 3 min by CAG. Several studies found that 43–54% of patients with MINOCA had coronary vasospasm, and it was recommended that all MINOCA

patients have a coronary vasospasm provocation test [25, 26]. The diagnosis of acute pulmonary embolism should be considered in MINOCA, but the value of this diagnosis as a routine screening is not obvious. In patients with secondary MINOCA, Collste et al. [38] found no pulmonary embolism on traditional pulmonary angiography CT. Therefore, regarding this diagnosis as a standard assessment method in MINOCA, pulmonary arteriography is not appropriate and suspected cases should be clinically maintained. Finally, endocardial biopsies are conducted in patients with suspected myocarditis (Fig. 2).

Prognosis

Comparisons of prognosis of MINOCA and MI-CAD patients are challenging because of the variations in the relevant pathophysiological mechanisms. MINOCA is a group of syndromes with multiple causes, the prognosis of MINOCA and its associated factors are broadly concerned with, and the prognosis is closely related to the cause of disease, which should be actively investigated. In a systematic review, the 12-month all-cause mortality rate of patients with MINOCA was found to be 4.7% [2]. A meta-analysis of MINOCA and MI-CAD clinical manifestations and prognosis showed a high risk for adverse events in patients with MINOCA. The rates of 1-year all-cause mortality, MI, all-cause mortality + MI, cardiac death, and MACE were 2.4, 1.2, 4.0, 1.4, and 9.2%, respectively [39]. Another study showed that after 25 months of follow-up, the mortality rate of MINOCA patients was 3.8%. Even though MINOCA's long-term prognosis is better than MI-CAD, it is not a benign condition [40]. A large sample study of 14,045 patients with MINOCA indicated that their mortality rate was higher than that of MI-CAD patients within 30 days (4.48 and 3.46%, respectively) [41]. The GENESIS-PRAXIS study revealed that, despite the absence of obstructive CAD, MINOCA patients have high-risk characteristics. Approximately 14% of MACE occur within 1 year of follow-up [9]. The KAMIR-NIH study found that there was no difference between the prognosis of MINOCA and MI-CAD patients in 2 years of follow-up (9.1 and 8.8%, respectively), as well as no significant difference in CV death, noncardiac death, and reinfarction between 2 groups [42]. The COAPT study [3] revealed a 1-year mortality/re-MI rate in MINOCA patients of 5.3% and a 5-year mortality rate of 10.9%. A large retrospective study in Sweden showed that the rate of readmission for MI of patients with MINOCA was 6.3% within 17 months of follow-up [43]. A Korean MI registry study found that the 1-year all-cause mortality rate of patients with MINOCA was the same as that of CAD patients with single-/double-vessel stenosis (2.6 vs. 2.2%, $p = 0.952$) [44]. A large-scale, long-term Italian study showed that the incidence of MACE in MI-CAD patients was higher than in MINOCA patients after 26 months of follow-up, but that the rates of mortality, cardiogenic readmission, and stroke were similar [45]. A 2-year follow-up study indicated that MINOCA is widespread, with about half the MACE accompanying MI-CAD, and an all-cause mortality rate of 4.9%, mainly non-CV (4.5%) [7]. Another 3.8-year follow-up study [46] disclosed that the all-cause mortality rate for MINOCA was 12.1%, with a CV mortality rate of 5.3%, a respiratory mortality rate of 1.3%, and a tumor mortality rate of 3.1%. Of these, male sex, previous heart failure, and chronic obstructive pulmonary disease (COPD) were adverse factors in MINOCA prognosis, suggesting that lung disease and tumors are significant causes of death in MINOCA patients. The VIRGO study [47] showed that MINOCA and MI-CAD patients had comparable mortality, functional status, and psychosocial outcomes in the 1st and 12th months of follow-up (1st month: 1.1 vs. 1.7%, $p = 0.43$; 12th month: 0.6 vs. 2.3%, $p = 0.68$). Patients with MINOCA have higher rates of short-term survival than patients with STE-ACS, and a similar or worse long-term prognosis. The short- and long-term survival rates of MINOCA patients are lower than in the general population [48]. One research reported poor prognosis in elderly MINOCA patients undergoing CAG, with 1/5 presenting serious adverse events in 12 months [12]. A recent study on Chinese MINOCA patients found that although the incidence of MACE was lower than in MI-CAD patients, there was no significant difference in mortality after 1 year of follow-up [49]. More notably, the results from the SWEDEHEART registry showed that 23.9% of MINOCA patients experienced MACE over a 4-year follow-up [50]. In a survey of 1,220 AMI patients, Rhew et al. [51] found that MINOCA accounted for 8.2%, and there was no significant difference between the 2 groups, i.e., those with coronary stenosis >50% versus <50%, at 1 and 12 months in the occurrence of MACE ($p > 0.05$). Even though there is no obvious coronary stenosis in MINOCA patients, most of them have different degrees of heart injury and are still at a high risk for adverse CV events. This should be treated with full caution.

Predictors of Outcome

Studies on MINOCA's prognostic risk factors are minimal, and it is not clear if they differ from MI-CAD predictive risk factors. A current study has shown that reduced LV ejection fraction, nonobstructive CAD, β-blockers during follow-up, and ST depression on ECG at admission are independent predictors of the long-term prognosis of MINOCA patients [40]. Ciliberti et al. [52] reported that only 3-vessel disease, left main stem involvement, and elevated C-reactive protein were independent predictors of MACE in MINOCA patients during a 7-year follow-up period. Another study [53] revealed that hs-cTn levels constitute an independent risk factor for MACE events in MINOCA patients. The ACUITY trial [54] indicated that elevated cTn is associated with increased mortality in MINOCA. The KAMIR-NIH study [42] concluded that, in MINOCA patients, old age, traditional symptoms, STE on ECG, Killip Class IV, and diabetes were independent predictors of all-cause death at the 2-year follow-up. Another study [55] revealed that female sex, younger age, STE, atrial fibrillation, and a history of previous MI were independent predictors of MINOCA. A recent study [56] on prognostic risk factors for MINOCA during a 4.5-year follow-up reported that age, hypertension, diabetes, smoking, previous stroke, MI, peripheral vascular disease, COPD, decreased LV ejection fraction, lower total cholesterol levels, and higher creatinine levels were independent predictors of MACE. Current research on Chinese MINOCA patients reports that the independent predictors of MACE in MINOCA patients are older age, female sex, atrial fibrillation, and reduced LV ejection fraction [49]. Considering the variability in the MINOCA population, it would be an advantage to be able to determine MINOCA patients at risk of CV outcomes by means of clinical risk predictors.

Current Management

Since MINOCA has many possible pathological mechanisms, it is not certain that the classical secondary prevention and treatment strategy for type 1 MI are suitable for MINOCA patients. At present, there are no specific clinical guidelines or treatment recommendations. Recently, in a large-scale observational study in Sweden, Lindahl et al. [50] found that the proportion of patients on statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), β-blockers, and dual antiplatelet therapy (DAPT) was 84.5, 64.1, 83.4, and 66.4%, respectively. During an average follow-up of 4.1 years, 23.9% of the patients experienced MACE. For patients treated with statins, ACEI/ARB, or β-blockers, the hazard ratio (HR) (95% confidence interval [CI]) for MACE was 0.77 (0.68–0.87), 0.82 (0.73–0.93), and 0.86 (0.74–1.01), respectively. The HR of patients on DAPT was 0.90 (0.74–1.08) after a 1-year follow-up. The results of this study showed that MINOCA treatment with statins or ACEI/ARB has a long-term beneficial effect on the outcome, and β-blocker treatment a positive trend, but that DAPT has a neutral effect. The KAMIR-NIH [42] study showed that the use of renin-angiotensin inhibitor blockers (ACEI) and statins for MINOCA patients during a 2-year follow-up was associated with reduced mortality. Results from the EMMACE-2 study [57] showed that the use of ACEI in patients with MINOCA was significantly associated with a reduction in 6-month mortality (HR 0.31, 95% CI 0.03–0.78, $p < 0.004$). On the contrary, some research has demonstrated that statins do not reduce MACE in MINOCA patients [58]. Ishii et al. [59] found that in patients with MINOCA, long-term use of aspirin after discharge could not reduce adverse CV events. Other studies have shown that intensive clopidogrel therapy tends to be associated with an increased risk of CV mortality, MI, and stroke in MINOCA patients. Antiplatelet treatment can also be harmful to MINOCA patients, so it should not be routinely used [60]. Because of the diverse etiology and prognosis, the key to the treatment of MINOCA is to identify the etiology. On March 27, 2019, the American Heart Association (AHA) released guidelines for the diagnosis and management of MINOCA [24]; according to the recommendations, risk stratification and the most appropriate treatment scheme should be selected on the basis of etiology. For MINOCA patients with plaque rupture, DAPT is recommended for 1 year, and single antiplatelet therapy is recommended for life to those suspected of or diagnosed with plaque rupture and MINOCA. If only a mild degree of atherosclerosis is found on CAG, statins are also recommended [61]. MINOCA caused by coronary spasm can be treated with calcium-channel blocker (CCB) and nitrates. Montone et al. [28] found that patients who had been screened for coronary spasm stimulation and received CCB had a better prognosis than the control group, i.e., CCB was a robust secondary preventive measure. CCB has been indicated for MINOCA patients with coronary spasm in other trials [26]. Coronary dissection treatment is usually accompanied by intraluminal complications. Due to its inconspicuous appearance on CAG, diagnosis is easy to miss, and most dissections are not associated with atherosclerotic

disorders, so some researchers have indicated that traditional statin therapy should not be prescribed [62]. The treatment should be performed in clinical work according to the location of the dissection and the size of the blood vessels. If there is no obvious blood flow obstruction, conservative treatment is generally recommended, because coronary intervention and stenting may also lead to dissection and risk expanding the original range of the lesion. Other strategies may also play a role in patients with chronic pain and Takotsubo cardiomyopathy, e.g., antidepressants. Changes in lifestyle including weight loss, smoking cessation, a high-fiber diet, increased consumption of fruits and vegetables, and sport are also beneficial for the prognosis of MINOCA patients [63].

Conclusion

The incidence of MINOCA in the AMI population is 1–15%. MINOCA is a group of heterogeneous diseases arising from a variety of potential causes. CMR, OCT, IVUS, and left ventriculography are essential diagnostic tools. Although there is no obvious coronary stenosis in MINOCA patients, most have different degrees of heart injury and are still at a high risk of adverse CV events, and to be treated with full caution. Given that the treatment and prognosis are firmly identified with the pathogenesis, it is particularly important to discover the causes of the disease effectively. While it has been shown that the use of statins and ACEI/ARB to enhance MINOCA patients' long-term prognosis has significant benefits, aspirin, clopidogrel, and β-blocker medications have shown no improvement in prognosis for MINOCA patients. Indeed, there is an ongoing randomized clinical trial (EudraCT No. 2018-000889-11; ClinicalTrials.gov ID: NCT-03686696) evaluating the potential effects of ACE/ARB on a large scale should provide valuable information about the central principles for the management of MINOCA, including the benefits and potential risks. The advancement of multicenter research into the potential diagnosis and treatment of MINOCA will guide therapy and enhance the prognosis of patients.

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Author Contributions

All authors contributed to the study design. Based on discussions with all authors, Dr. Fuad A. Abdu drafted the manuscript, which all authors revised. All authors approved the final version submitted for publication.

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