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Myocardial Infarction with Nonobstructive Coronary Arteries

H.R. Reynolds and N.R. Smilowitz

Leon H. Charney Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA; email: harmony.reynolds@nyulangone.org

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myocardial infarction, nonobstructive coronary arteries, MINOCA, coronary spasm, takotsubo syndrome, myocardial injury

Abstract

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is an important subtype of myocardial infarction (MI) that occurs in approximately 6–8% of patients with spontaneous MI who are referred for coronary angiography. MINOCA disproportionately affects women, but men are also affected. Pathogenesis is more variable than in MI with obstructive coronary artery disease (MI-CAD). Dominant mechanisms include atherosclerosis, thrombosis, and coronary artery spasm. Management of MINOCA varies based on the underlying mechanism of infarction. Therefore, systematic approaches to diagnosis are recommended. The combination of invasive coronary angiography, multivessel intracoronary imaging, provocative testing for coronary spasm, and cardiac magnetic resonance imaging provides the greatest diagnostic yield. Current clinical practice guidelines for the secondary prevention of MI are based largely on data from patients with MI-CAD. Thus, optimal medications after MINOCA are uncertain. Clinical trials focused on the treatment of patients with MINOCA are urgently needed to define optimal care.

BACKGROUND, HISTORY, AND DEFINITIONS

The pathophysiology, management, and outcomes of acute myocardial infarction (MI) vary based on the presence or absence of obstructive coronary artery disease (CAD) or coronary dissection at the time of invasive coronary angiography. This review focuses on the syndrome of myocardial infarction with nonobstructive coronary arteries (MINOCA), an MI characterized by the absence of 50% or greater stenosis in all major epicardial coronary arteries upon coronary angiography. This clinical syndrome encompasses patients with no coronary atherosclerosis and those with mild to moderate nonobstructive atherosclerotic disease.

The first cases of MINOCA were reported nearly a century ago, based on pathological evaluation of the coronary arteries in autopsy series of decedents with fatal MI and no obstructive coronary atherosclerosis (1, 2). In early angiographic studies of patients with acute MI, DeWood and colleagues identified nonobstructive coronary disease in ~3% of patients (3, 4).

For many years after its first clinical description, MINOCA was a loosely defined clinical entity without a standard nomenclature or widespread acceptance in the cardiovascular community. The term MINOCA was coined in 2013 by Dr. John Beltrame (5). Scientific statements, consensus documents, clinical practice guidelines from multiple cardiovascular societies, and the Fourth Universal Definition of MI have aligned to establish uniform diagnostic criteria for MINOCA and differentiate it from MI with obstructive CAD (MI-CAD) (6–10). MINOCA is a provisional diagnosis assigned at the time of coronary angiography in patients who meet criteria for the Universal Definition of MI, with a <50% diameter stenosis in all major epicardial coronary arteries, and in the absence of a specific alternative cause for the clinical presentation, such as myocarditis or pulmonary embolism (7).

EPIDEMIOLOGY

In the United States, ~800,000 men and women are hospitalized with acute MI annually, and among these, an estimated 65,000 have MINOCA (11). The syndrome occurs in approximately 6–8% of patients with spontaneous MI who are referred for coronary angiography, and it is substantially more common among female MI patients than male MI patients (12–15). Among patients without a history of obstructive CAD, MINOCA was identified in 10.5% of women and 3.4% of men included in a large quality-improvement registry in the United States (13). Due to the large number of males who experience MI, the proportion of MINOCA patients who are female is approximately 40–60%. The prevalence of MINOCA is higher in Black patients (10.5%) than in those of White race (5.4%) or Hispanic ethnicity (6.8%) (13).

Seasonal and circadian peaks in MINOCA incidence largely follow patterns observed for MI in general. A somewhat higher proportion of MINOCA cases occurs in summer and fall, and there is a peak in MINOCA presentations in morning hours, with a secondary peak among women in late afternoon (16, 17).

CLINICAL PRESENTATION

Clinical presentations of MINOCA are often indistinguishable from MI-CAD. Most patients with MINOCA (83.1%) present with non-ST segment elevation MI (NSTEMI), but ST segment elevations can occur and are associated with increased risk of in-hospital mortality (13). Female sex and younger age are independently associated with a diagnosis of MINOCA (18). The prevalences of traditional cardiovascular risk factors, including dyslipidemia, diabetes mellitus, and tobacco use, are lower in patients with MINOCA compared to MI-CAD (13, 19). However, 75% of MINOCA patients have at least one traditional cardiovascular risk factor (13, 20). On average,

patients with MINOCA tend to have lower peak cardiac troponin concentrations than patients with MI-CAD, but there is wide variability (13).

IN-HOSPITAL OUTCOMES

The prognosis after MINOCA is more favorable than after MI-CAD (15). Still, MINOCA can be fatal, and prehospital deaths with histologic evidence of acute MI and nonobstructive coronary arteries have been reported in the modern era (21). Patients with MINOCA can develop cardiogenic shock, ventricular arrhythmias, and in rare cases, mechanical complications such as rupture (7, 14, 22, 23). In-hospital mortality associated with MINOCA is ~1% (13, 19). The composite of in-hospital death, reinfarction, cardiogenic shock, or heart failure occurs in 4.9% of patients (13).

POST-DISCHARGE OUTCOMES

The post-discharge prognosis of patients after MINOCA is worse than for patients without MI but more favorable than after MI-CAD (15, 19, 24–26). Outcomes of MINOCA patients with nonobstructive plaque were poorer than outcomes of patients with angiographically normal coronary arteries in some studies and similar in others, after adjustment for comorbid conditions and demographics (15, 24, 27).

Short- and Long-Term Mortality

At 1-year follow-up, MINOCA mortality is 2–5% (12, 13, 15, 19, 27, 28). Among individuals age 65 and older, the risk of adverse outcomes is higher still, with up to 12% mortality at 1-year follow-up (28). In a longitudinal cohort study of 9,136 MINOCA patients identified in the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy) registry, 4-year all-cause mortality was 13.4% (29). In a separate study of 2,092 patients with MINOCA in Canada, mortality was ~11% at 5 years (19). In line with this figure, a systematic review identified an annual mortality rate of 2.2% (27).

Reinfarction

Reinfarction occurs in 1.3–2.6% of patients by 1 year (15, 28), and 7.1% at 4 years (29). Within SWEDEHEART, ~60% of patients with reinfarction after MINOCA underwent coronary angiography. Of these, half had progression of coronary atherosclerosis with >50% stenosis at the time of the second MI, consistent with MI-CAD, a frequency that was consistent whether the second event occurred within the first year after the initial MINOCA or more than 5 years later (30). Reinfarction after MINOCA conferred increased risk: 21.6% of these patients died over median 38-month follow-up, with no difference in mortality among those with and without progression of atherosclerosis (30).

Major Adverse Cardiovascular Events

Major adverse cardiovascular events (MACE), including all-cause mortality as well as hospitalization for MI, ischemic stroke, or heart failure, occur at a substantial rate in MINOCA patients. Clinicians should follow patients with MINOCA closely in the years after discharge, as with other MI patients. In a pooled analysis of patient-level data from eight NSTEMI trials, death or MI at 30 days was 2.2% in participants with MINOCA (31). A meta-analysis identified a 1-year MACE rate of 9.6% in >30,000 patients (15). Within the American College of Cardiology

National Cardiovascular Data Registry (NCDR) Cath-PCI Registry, the 1-year rate of MACE was 19% in patients aged 65 or older (28). Death or MI occurred in 11.1% of MINOCA patients at 2 years after the event in a New Zealand cohort study (19, 24). MACE occurred in nearly 25% of individuals of all ages with MINOCA at 4-year follow-up in SWEDEHEART (29).

Risk Factors for Adverse Outcomes

Risk factors associated with long-term MACE after MINOCA appear to be similar to those associated with poor outcomes after MI-CAD, including ST-segment elevation on the presenting electrocardiogram (ECG), older age, reduced left ventricular ejection fraction, diabetes mellitus, hypertension, tobacco use, prior MI, stroke, peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and lower total cholesterol (32, 33). Inflammation, as measured by C-reactive protein during the index admission, and elevated remnant cholesterol are associated with long-term all-cause mortality and MACE in patients with MINOCA (34, 35). Peak troponin was also associated with long-term outcomes in the SWEDEHEART registry (36). In a Chinese series of 633 patients with MINOCA, a diagnosis of depression at the time of MINOCA was also associated with an increased hazard for MACE (37).

Prediction of long-term risk after MINOCA is suboptimal. The Global Registry of Acute Coronary Events (GRACE) 2.0 risk score provided reasonable discrimination to predict 1-year mortality in MINOCA patients in the SWEDEHEART registry (c-statistic 0.750) but had poorer accuracy for the prediction of the composite of 1-year death or MI (c-statistic 0.685). The prognostic accuracy of the GRACE 2.0 risk score was inferior among patients with MINOCA compared to MI-CAD patients (38). Improved approaches to long-term risk stratification after MINOCA are necessary.

Quality of Life

Physical capacity and quality of life are diminished after MINOCA. Nearly 25% of MINOCA patients reported angina at 1 year after MI in the large TRIUMPH (Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health) registry, similar to the proportion of patients with MI-CAD (39). Quality-of-life scores on the Seattle Angina Questionnaire were worse at 1 year after MI among MINOCA versus MI-CAD patients. In a series of MINOCA patients from Sweden, physical capacity measured by bicycle exercise stress testing 6 weeks after MI was worse than in age- and sex-matched healthy controls but better than in matched MI-CAD patients (40). Despite this, at 3-month follow-up after MI, patients with MINOCA reported worse mental health dimensions of quality of life compared to patients with MI-CAD, similar to the poorer mental and physical health status scores observed at 1 year after MINOCA in the TRIUMPH study (39, 40). In a multicenter study in North America, women with MINOCA were less likely to report high stress levels at the time of presentation and at 2 months post-MI compared to women with MI-CAD (41).

PATHOGENESIS

The pathogenesis of MINOCA is heterogeneous and can include atherosclerotic plaque rupture, plaque erosion, coronary thromboembolism, coronary spasm, and rarely, coronary dissection (**Figure 1**) (7). In some cases, patients may have a provisional diagnosis of MINOCA but are ultimately assigned a diagnosis of takotsubo syndrome, acute myocarditis, or nonischemic cardiomyopathy after additional testing. These patients are not considered to have MINOCA once a nonischemic alternate diagnosis has been established (7).

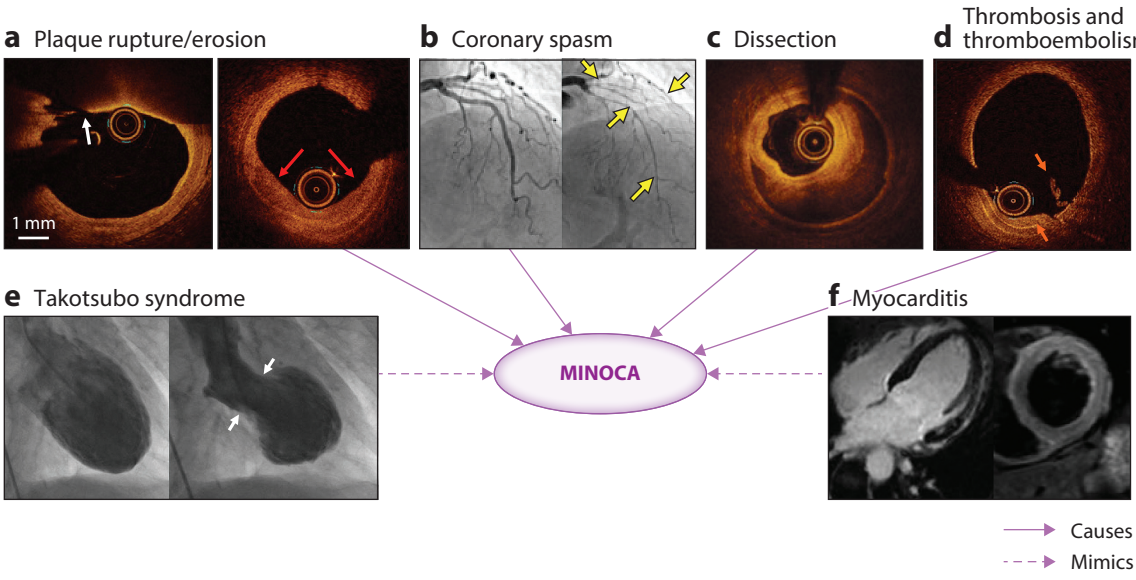

Figure 1

Causes (*solid arrows*) and mimics (*dotted arrows*) of myocardial infarction with nonobstructive coronary arteries (MINOCA). The pathogenesis of MINOCA is heterogeneous; its vascular etiologies can include (*a*) atherosclerotic plaque rupture (rupture site, *white arrow*) or erosion (with thrombus, *red arrows*), (*b*) coronary spasm (*yellow arrows*), (*c*) coronary dissection, or (*d*) thrombosis and thromboembolism (*orange arrows*). Takotsubo syndrome (*e*) and myocarditis (*f*) are the most common mimics of MINOCA and should be excluded by cardiac magnetic resonance imaging.

Atherosclerotic Plaque Rupture and Erosion

Coronary atherosclerosis is a common cause of MINOCA, as demonstrated by intracoronary imaging studies. Culprit atherosclerotic plaques in MINOCA are typically smaller than in patients with obstructive MI-CAD and are rarely outwardly remodeled (42, 43). Plaque rupture exposes tissue factor and thrombogenic contents of the lipid-rich necrotic core to the bloodstream, promoting local thrombus formation (44). Plaque erosion, another potential atherosclerotic mechanism of MINOCA, is characterized by thrombus formation overlying a site of denuded surface endothelium that in turn overlies fibrous plaque, rather than lipidic plaque (45).

There are several potential mechanisms by which plaque rupture and erosion can lead to MINOCA: transient occlusion of the vessel at the rupture site before intrinsic thrombolysis, distal embolization of some or all of the thrombus with small-vessel occlusion that is not angiographically evident, or flush occlusion of the ostium of a side branch that is similarly not apparent by invasive angiography. In some cases, thrombus may be identified only in retrospect, such as after cardiac magnetic resonance imaging (CMRI) demonstrates an infarction in a corresponding coronary territory. Such patients may receive an initial diagnosis of MINOCA that ultimately proves to be incorrect.

In clinical practice, intravascular imaging is essential to visualize plaque rupture, thrombus, or culprit plaques in various stages of healing after rupture, including intraplaque cavities and healing layered plaques (43, 46, 47).

Coronary Artery Embolism

Coronary artery embolism is a cause of MINOCA. Intracardiac thrombus can form in the left atrium, left atrial appendage, or left ventricle in the setting of stasis from atrial fibrillation, left

ventricular dysfunction, or left ventricular noncompaction. Subsequent migration of thrombus to the epicardial coronary arteries can cause MI. When such an embolism results in occlusion of a large coronary vessel, it is categorized as MI-CAD. Alternatively, occlusion of a small-caliber distal vessel or branch vessel may not be appreciated on coronary angiography, thereby resulting in a clinical diagnosis of MINOCA. Paradoxical embolization through an atrial septal defect or patent foramen ovale may also cause MINOCA (48).

Coronary Artery Spasm

Coronary artery spasm is a common mechanism of MINOCA. Among patients with MINOCA who underwent routine provocative testing with intracoronary acetylcholine or ergonovine, 24–70% showed evidence of epicardial or microvascular coronary spasm (46, 49–56). Epicardial spasm is defined by vasoconstriction of at least 90% in response to provocation testing (57). Microvascular spasm is defined by recapitulation of symptoms with ECG changes in response to a provocation without epicardial spasm (58). In a series of 80 consecutive MINOCA patients among whom 37 (46.2%) had evidence of coronary spasm, epicardial spasm was diagnosed in 24 and microvascular spasm was diagnosed in 13 individuals (49). Any coronary spasm was associated with a higher risk of long-term mortality (32.4% versus 4.7%, $p = 0.002$), and epicardial spasm was associated with poorer outcomes than microvascular spasm (49). In a separate series of 40 patients who did not have intravascular imaging evidence of a high-risk coronary culprit to explain the MINOCA presentation, 38% had a positive provocation test for coronary spasm (46). Abnormal coronary reactivity is also frequently observed in patients with angiographic evidence of myocardial bridging, a finding that was more common in patients with MINOCA than in stable patients with no obstructive CAD (21.3% versus 7%, $p = 0.002$) (59). Acetylcholine provocation testing results are particularly likely to be abnormal in MINOCA patients with myocardial bridges, up to 88% (30/34) in one series (59). Myocardial bridging is not thought to be a cause of MINOCA on its own (60). In addition, coronary spasm and atherosclerotic culprit lesions may coexist in the same patient and even in the same coronary segment (43, 47). Given the prevalence of coronary spasm in MINOCA, spasm may be inferred as the cause of MINOCA in the absence of dedicated provocative testing when infarct or regional edema is observed by CMRI and no coronary culprit lesion is identified by intracoronary imaging (43).

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) is an uncommon cause of MINOCA (43). In SCAD, the spontaneous development of an intramural hematoma narrows the true lumen, occludes side branches, or both, leading to MI. Although SCAD is not atherosclerotic, it frequently appears as a severe coronary narrowing on coronary angiography and therefore is an angiographic diagnosis that is not consistent with MINOCA. In some cases, this may be mistaken for MI due to atherosclerosis or thrombosis (61). However, the narrowing may improve prior to coronary angiography, or may not be appreciated, leading to a diagnosis of MINOCA. Diagnosis of SCAD requires a high index of suspicion and careful attention to angiographic review. An intimal tear may or may not be present. Intracoronary imaging should be considered in selected cases when the diagnosis is uncertain based on angiography. Among patients with SCAD, the overwhelming majority (90%) are women, the mean age is ~50 years, and traditional cardiovascular risk factors are uncommon, characteristics that tend to overlap with the broader population of patients at risk for MINOCA (62, 63). In fact, SCAD accounts for nearly 35% of MI occurring in women age ≤50 years (64). Consequently, it should be considered routinely in the differential diagnosis of MINOCA.

Coronary Microvascular Disease

The coronary microcirculation may theoretically contribute to the development of MINOCA, due to either a fixed resistance or failure to vasodilate in the setting of increased myocardial oxygen demand. Coronary artery spasm frequently coexists with coronary microvascular disease (65). The prevalence of coronary microvascular disease in MINOCA is difficult to establish because testing is performed after an MI event has occurred, and the myocardial edema associated with MI has the potential to impact microvascular function. This is frequently observed in MI-CAD, where an abnormal index of microcirculatory resistance is an adverse prognostic indicator (66). Nonischemic myocardial edema may also affect coronary microvascular function (67). In a study of 30 patients with MINOCA and 10 age- and sex-matched patients with noncardiac chest pain, coronary flow velocity ratios measured in the left anterior descending coronary artery in response to adenosine were significantly lower in patients with MINOCA during hospitalization and 1 month later (68). Additional investigation is needed to define the contribution of coronary microvascular disease to MINOCA pathophysiology.

Type 2 Myocardial Infarction and Supply–Demand Mismatch

Perturbations of myocardial oxygen supply and demand can lead to MI, including in the absence of plaque rupture or angiographically obstructive CAD. This may occur in the setting of hypotension, hypertension, tachycardia, bradycardia, or profound anemia, with or without epicardial or microvascular CAD. MI events due to supply–demand mismatch related to such perturbations in the absence of obstructive CAD are sometimes considered under the heading of MINOCA. However, the term MINOCA is best reserved for MI due to a vascular phenomenon.

MIMICS OF MYOCARDIAL INFARCTION

Several cardiac conditions associated with chest discomfort and elevation in troponin concentration, most notably takotsubo syndrome, myocarditis, and pulmonary embolism, can mimic a clinical presentation of MI. These conditions may be misclassified as MINOCA. Therefore, it is imperative that clinical providers routinely pursue diagnostic testing to identify the non-MI mimics described herein.

Takotsubo Syndrome

Takotsubo syndrome is a reversible syndrome of left ventricular dysfunction that can mimic the presentation of acute MI, with elevated troponins, ischemic ECG changes, and symptoms. Typically, takotsubo syndrome occurs in postmenopausal women, is preceded by a physical or emotional stressor, and results in left ventricular wall motion abnormalities that are out of proportion to the peak troponin concentration (69). B-type natriuretic peptide is generally elevated. The pathophysiology of takotsubo syndrome is incompletely understood, but it is not believed to be caused by atherosclerotic vascular disease and is therefore considered distinct from MI. The dominant mechanisms appear to be neurohormonal stunning and/or microvascular spasm, and the autonomic nervous system is an important contributor to pathophysiology. Some patients may have a form of hypertrophic cardiomyopathy with dynamic outflow tract obstruction and increased afterload as a cause of or contributor to takotsubo syndrome (70). Careful review of coronary angiography is paramount in patients with suspected takotsubo syndrome, because SCAD of the left anterior descending coronary artery has been reported after expert angiographic review in a small proportion of these patients (71, 72). Once a diagnosis of takotsubo syndrome has been confirmed, the term MINOCA no longer applies.

Myocarditis

Myocarditis is a common cause of chest pain and troponin elevation in patients assigned a provisional diagnosis of MINOCA. In a recent systematic review of 27 studies including 2,866 patients with MINOCA who had CMRI, myocarditis prevalence was 34.9% [95% confidence interval (CI) 27.8–42.4%] (73). In a patient data meta-analysis of nine studies, angiographically normal coronary arteries were associated with a higher pooled prevalence of myocarditis than nonobstructive CAD (51% versus 23%, $p < 0.001$, age- and sex-adjusted odds ratio 2.30, 95% CI 1.12–4.71). Younger MINOCA patients and men were more likely to have myocarditis than women and older individuals (73). In a separate study of patients with a provisional diagnosis of MINOCA, STEMI at presentation was not associated with a higher prevalence of myocarditis assessed by CMRI (74). A final diagnosis of myocarditis supersedes the provisional pre-CMRI MINOCA designation. However, it should be noted that coronary artery spasm is sometimes observed in cases of CMRI-confirmed myocarditis.

Pulmonary Embolism

Pulmonary embolism (PE) should be considered in all patients with a provisional diagnosis of MINOCA, because PE is a potentially life-threatening diagnosis that can cause chest pain, dyspnea and elevated troponin concentrations. A history of recent immobility, long-distance travel, surgery, cancer, or calf pain may be helpful clues to identify individuals at high likelihood of PE. Unexplained tachycardia, tachypnea, or hypoxia should prompt D-dimer measurement or computed tomography pulmonary angiography to assess for this alternate diagnosis before or after coronary angiography. Even in patients without these signs, the potential diagnosis of PE should be entertained in the setting of MINOCA. However, in a series of 100 patients with MINOCA who underwent routine computed tomography pulmonary angiography, none had PE (75).

Thrombophilia

Hereditary thrombophilia may contribute to MINOCA pathogenesis. In a pooled analysis of eight studies that reported results of screening for inherited thrombophilia in patients with MINOCA, 14% of patients had an inherited thrombotic disorder, with factor V Leiden in 12%, protein C or S deficiency in 3%, and factor XII deficiency in 3% (12). Acquired thrombophilia may also play a role. In a study of 84 MINOCA patients who underwent systematic workup for thrombophilia >3 months after MI, antiphospholipid syndrome was identified in 15.5% and inherited thrombophilia in 23.8% (76).

DIAGNOSTIC APPROACHES

The optimal management of MINOCA is expected to vary based on the underlying mechanism of infarction. A systematic approach to evaluation is crucial to confirm the diagnosis of MI and to identify the underlying pathophysiology. A clinical algorithm was proposed in the 2019 American Heart Association Scientific Statement on MINOCA for this purpose (**Figure 2**) (7). This algorithm emphasizes careful review of coronary angiography, routine assessment of left ventricular function with echocardiography or ventriculography, and contrast-enhanced CMRI to diagnose myocarditis or identify the territory of acute MI or injury (7, 8, 77). The current European Society of Cardiology guidelines on management of non-ST segment elevation acute coronary syndromes include a section on MINOCA with a similar recommended diagnostic algorithm, the use of which is a class I recommendation (77). Intracoronary imaging with optical

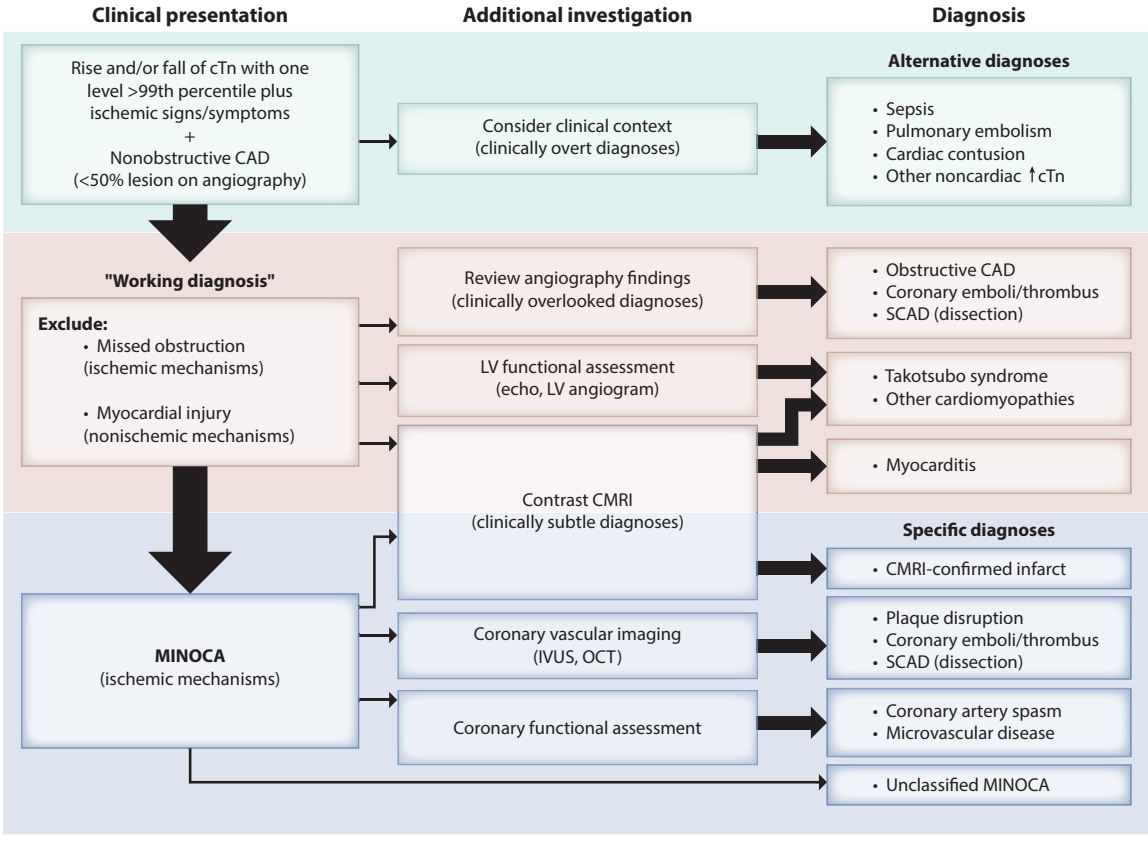

Figure 2

Clinical algorithm for the diagnosis of MINOCA from the 2019 American Heart Association Scientific Statement on MINOCA. Abbreviations: CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; cTn, cardiac troponin; IVUS, intravascular ultrasound; LV, left ventricular; MINOCA, myocardial infarction with nonobstructive coronary arteries; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection. Figure adapted from Reference 7 with permission.

coherence tomography (OCT) or intravascular ultrasound (IVUS) should be considered at the time of diagnostic coronary angiography to identify atherosclerotic culprit lesions. Some operators may prefer to employ OCT as a separate diagnostic procedure, for example after CMRI has identified an area of late gadolinium enhancement or regional myocardial edema, or at a minimum has ruled out myocarditis (52). Testing for microvascular or epicardial coronary spasm may also be considered because results could alter long-term medical therapy (7).

Diagnostic approaches that integrate the results from multi-modality imaging are most likely to provide insights into MINOCA pathophysiology (43, 52, 78, 79). In an international multicenter prospective study of 145 women with a provisional diagnosis of MINOCA, multivessel coronary OCT and CMRI identified a cause of the clinical presentation in 84.5% of patients. Among these patients, 75.5% of presentations were ischemic and 24.5% were nonischemic (e.g., myocarditis) (43). Intracoronary imaging with OCT identified a culprit lesion in 46% of patients, with atherosclerotic mechanisms, such as intraplaque hemorrhage, layered plaque, and plaque rupture, the most common findings. Few patients had plaque erosion upon OCT, and only one case of SCAD was observed (43). Spasm testing was not part of the study protocol.

In a separate series of 40 highly selected patients with MINOCA, ECG evidence of ischemia, and corresponding wall motion abnormalities who underwent OCT and CMRI, the prevalence of coronary culprit lesions by OCT was 80%; 35% had plaque rupture, 30% had plaque erosion, and 3% had calcified nodules (52). In this study, CMRI findings consistent with MI were evident in 78% of MINOCA patients, and integrating CMRI and OCT findings identified a definitive mechanism of MINOCA in all cases (52). In a single-center Polish study of 38 MINOCA patients who underwent multivessel coronary OCT, including 55% women and 39% with STEMI, plaque disruption or coronary thrombus was present in 29% of cases (78). Among 31 patients who underwent CMRI, 23% had evidence of late gadolinium enhancement indicative of MI, which was more common in patients with a coronary culprit identified by OCT. Infarct-related arteries (IRAs) were more likely to have OCT evidence of plaque disruption, thrombus, and thin-cap fibroatheroma than non-IRAs (78).

In a cohort of 82 consecutive MINOCA patients who underwent OCT at a single center in Japan, 51.2% had a high-risk culprit lesion, including ruptured plaque (15.9%), calcified nodule (11.0%), SCAD (8.5%), lone thrombus (8.5%), thin-cap fibroatheroma (6.1%), and plaque erosion (1.2%) (46). A greater number of events was observed over long-term follow-up in patients with versus without a high-risk culprit lesion (10% versus 0%, $p = 0.040$) by OCT (46).

In a series of 50 women with MINOCA, plaque disruption was identified in 38% of those who underwent IVUS (79). Culprit plaques were most likely to have fibrous (52.6%) or fibrofatty (31.6%) composition and tended to have a lower plaque burden than the largest plaque imaged in the culprit vessel. Only 21% of culprit plaques demonstrated outward remodeling (42). Plaque disruption was frequently associated with CMRI evidence of myocardial edema, without infarction (43, 79).

Practical Considerations Regarding Imaging

Intracoronary imaging with OCT or IVUS provides important insights in the diagnostic evaluation of patients with MINOCA. However, selecting which vessel(s) to image can be challenging, since the culprit vessel cannot be reliably identified in many cases. In prior studies of patients with MI-CAD, ST depressions and T wave inversions on ECG identified the correct culprit coronary vessel in only 60% and 84% of cases, respectively (80). In a study of 114 patients with NSTEMI who underwent invasive coronary angiography and blinded CMRI, the IRA was not identifiable by angiography in 37% of cases. Among patients in whom an IRA was assigned on the basis of coronary angiography, the culprit vessel did not match the infarct territory as determined by CMRI in 14% of cases, and another 13% had a CMRI diagnosis of a non-MI condition such as myocarditis. Since neither ECG criteria nor coronary angiographic findings reliably identify the culprit vessel in patients with MINOCA, multivessel intracoronary imaging may be necessary for maximal diagnostic yield (81).

Cardiac Magnetic Resonance Imaging

Although CMRI is essential to provide insights into MINOCA, delays from the onset of ischemic symptoms to CMRI, as well as the specific CMRI sequences obtained, can affect the diagnostic yield of this modality (43, 82). In a recent comparison between two prospective multicenter observational studies of MINOCA in Sweden, early CMRI with T1 and extracellular volume (ECV) mapping at a median 3 days post-MI yielded a diagnosis in 77% of MINOCA patients, versus 47% when CMR was performed at a median 12 days and without T1 and ECV mapping techniques (82). This study highlights the critical importance of timely CMRI in patients with MINOCA, ideally during the index hospitalization, since delays in imaging may lead to missed findings of

myocardial edema or myocarditis. Additionally, T1 mapping and ECV sequences in combination with T2 and late gadolinium enhancement imaging should be performed to provide optimal diagnostic discrimination in patients with MINOCA (43, 79). In a recent analysis of 36 women with MINOCA who underwent OCT imaging and had late gadolinium enhancement indicative of MI upon CMRI, the size of the infarct was not different in patients with versus without an OCT-defined coronary culprit lesion (83).

Provocative Testing for Coronary Spasm

Provocative testing for coronary spasm may be considered at the time of diagnostic angiography for MINOCA or during a subsequent invasive evaluation. Contemporary approaches to testing involve administration of a bolus dose or infusion of intracoronary acetylcholine or ergonovine. Escalating doses are administered until a >90% stenosis indicative of coronary spasm occurs (57). Despite concerns about the safety of provocative testing in the setting of acute MI, emerging data support the relative safety of coronary reactivity testing for spasm among patients presenting with MINOCA (55, 56, 59). In recent comparisons of intracoronary acetylcholine testing in MINOCA patients versus stable patients without recent MI, complications of testing occurred in 9–15% of cases. Frequencies of transient bradyarrhythmia (8–13%), supraventricular tachycardias or atrial fibrillation (1–3%), or transient hypotension (0–2%) were similar between MINOCA and stable patients (55, 56). Ventricular tachycardia and fibrillation were rare (<1%) complications of provocative testing (56). In a separate study, procedure-related arrhythmias were reported in ~5% of patients with recent MINOCA undergoing reactivity testing (49). None of the studies in MINOCA patients reported reinfarction or MACE attributable to provocative testing.

Coronary Computed Tomography Angiography

Although coronary computed tomography angiography (CCTA) can identify the presence and extent of coronary atherosclerosis, imaging resolution is not currently sufficient to identify culprit plaque rupture. In a series of 50 selected patients with MINOCA and a CMRI-confirmed area of late gadolinium enhancement consistent with MI, CCTA identified a greater number of atherosclerotic plaques than coronary angiography, with lesions in both IRAs and non-IRAs (84). In the IRAs, plaques were more likely to be noncalcified and have greater plaque area, despite no differences in the mean percent luminal stenosis (84). In a separate study, 57 patients with MINOCA diagnosed by CMRI did not have a greater burden of atherosclerotic disease detected by CCTA than healthy volunteers without known cardiovascular disease, matched by age and sex (85). In a study of 25 unselected patients with MINOCA, no coronary plaques were observed in 80% of patients, and only mild plaques were present in the remaining cases (86). Thus, the yield of CCTA in MINOCA is low and its role in the diagnostic evaluation of MINOCA is limited at present. One clinical scenario in which CCTA may be useful is to aid in the decision whether to prescribe statin therapy to a MINOCA patient with angiographically normal coronary arteries.

APPROACHES TO MANAGEMENT

Role of Revascularization

At present, the preferred treatment of MINOCA is medical therapy. Infrequently, intracoronary imaging in a patient with MINOCA may reveal a substantial plaque burden, and an operator may choose to perform percutaneous coronary intervention in these cases. The benefits of doing so remain unclear. Though this clinical scenario has never been specifically studied, a similar clinical syndrome is MI caused by thrombotic coronary occlusion due to erosion of

a small plaque. In plaque erosion, a strategy of medical management, with or without aspiration thrombectomy, but without stent placement, conferred excellent long-term outcomes (87, 88).

Medical Therapy

Clinical practice guidelines for the secondary prevention of MI are based largely on data from patients with MI-CAD (89). Specific medications for optimal secondary prevention of MINOCA are not known, and clinical trials dedicated to MINOCA patients are urgently needed. Consequently, medications for secondary prevention of MI are administered less often at the time of discharge after a diagnosis of MINOCA than MI-CAD, and with heterogeneity in clinical practice indicative of equipoise in the medical community (13, 90, 91). Although it stands to reason that the best treatment varies according to the underlying mechanism of MINOCA, the concept of targeted therapy in MINOCA has yet to be rigorously tested. Still, current European Society of Cardiology guidelines for the management of non-ST segment elevation acute coronary syndromes recommend the usual complement of secondary prevention medications for MINOCA when the specific underlying cause has not been identified (77).

In the absence of randomized controlled trials, observational studies provide key insights into the best medical therapy in MINOCA (29, 50, 92–95). In a propensity-matched analysis of 9,466 MINOCA patients in the SWEDEHEART registry, statins [adjusted hazard ratio (aHR) 0.77, 95% CI 0.68–0.87] and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) (aHR 0.82, 95% CI 0.73–0.93) were associated with lower rates of long-term MACE. Beta blockers (BB) were associated with a trend toward benefit (aHR 0.86, 95% CI 0.74–1.01), while no reduction in MACE was observed with dual antiplatelet therapy (aHR 0.90, 95% CI 0.74–1.08) (29). Data from smaller cohorts corroborate many of these observations. In an analysis of 396 patients with MINOCA from a prospective multicenter KAMIR-NIH (Korean Acute Myocardial Infarction Registry–National Institutes of Health) registry, nonuse of statins (HR 2.17, 95% CI 1.04–4.54) and ACEI/ARB (HR 2.63, 95% CI 1.08–6.25) was associated with higher 2-year mortality (50). In the EMMACE-2 (Evaluation of Methods and Management of Acute Coronary Events) registry of 350 patients with MINOCA, ACEI (OR 0.31, 95% CI 0.03–0.78), but not BB, prescribed at discharge were associated with lower 6-month mortality in MINOCA, although the sample size was small (92). Similar findings were reported in series from China ($n = 241$) and Italy ($n = 134$), in which use of ACEI/ARB, but not BB, was associated with decreased MACE (92, 93, 95). However, not all studies demonstrate a benefit of ACEI/ARB after MINOCA. In an Italian registry of 621 patients with MINOCA, use of BB, but not ACEI, was associated with reduced risk of MACE at long-term follow-up (94). Similarly, statin use was associated with favorable outcomes after MINOCA in many (29, 50, 93) but not all studies (94, 95). Consistent with data from SWEDEHEART, dual antiplatelet therapy at discharge after MINOCA has not been associated with reduced risks of MACE in any observational studies to date (29, 94).

Although administration of calcium channel blockers is reasonable in patients with coronary spasm as the presumed mechanism of infarction, its role in unselected patients with MINOCA remains uncertain. In an observational series from Italy, calcium channel blocker use at discharge was not associated with a lower incidence of MACE after MINOCA (94). Still, calcium channel blockers are typically recommended when the cause of MINOCA is not known or spasm testing has not been performed, particularly when there is postinfarct chest pain (7, 8, 77).

Although themes emerge from the observational studies evaluating secondary prevention of MINOCA, these findings are hypothesis-generating and require confirmation in large randomized trials. The MINOCA-BAT trial, a randomized evaluation of BB and ACEI/ARB treatment in

patients with MINOCA, is currently ongoing and seeks to enroll 3,500 participants to determine the effects of these two treatments on MACE (96). The StratMed-MINOCA trial plans to randomly assign 150 patients with MINOCA who have evidence of coronary microvascular disease to eplerenone versus usual care. The primary endpoint of this study is within-patient change in N-terminal pro-brain natriuretic peptide at 30 days and 6 months, and MACE will be evaluated as a secondary endpoint. The PROMISE trial will randomly assign 180 patients with MINOCA to a precision medicine approach with coronary OCT, CMRI, and coronary spasm testing to guide tailored medical therapy versus a standard approach to acute coronary syndrome management (97). Even after the completion of MINOCA-BAT, StratMed-MINOCA, and PROMISE, additional trials will be necessary to define optimal medical therapy after MINOCA.

CONCLUSIONS

MINOCA is an important MI subtype that occurs in approximately 6–8% of patients with spontaneous MI who are referred for coronary angiography. MINOCA disproportionately affects women, but men are also affected (12, 15). Pathogenesis is more variable than in MI-CAD. Dominant mechanisms include atherosclerosis, thrombosis, and coronary artery spasm. Since management of MINOCA varies based on the underlying mechanism of infarction, systematic approaches to diagnosis are recommended, and the combination of invasive coronary angiography, multivessel intracoronary imaging, provocative testing for coronary spasm, and CMRI provides the greatest diagnostic yield. Even when a provisional diagnosis of MINOCA is made, myocarditis remains possible, and CMRI should be performed routinely where available for this reason. Treatment is targeted to the most likely underlying diagnoses. Since current clinical practice guidelines for the secondary prevention of MI are based largely on data from patients with MI-CAD, optimal medications after MINOCA are uncertain. Clinical trials focused on the treatment of patients with MINOCA are urgently needed to define optimal care.

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