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AHA SCIENTIFIC STATEMENT

Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease

A Scientific Statement From the American Heart Association

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ABSTRACT: Myocardial infarction in the absence of obstructive coronary artery disease is found in ≈5% to 6% of all patients with acute infarction who are referred for coronary angiography. There are a variety of causes that can result in this clinical condition. As such, it is important that patients are appropriately diagnosed and an evaluation to uncover the correct cause is performed so that, when possible, specific therapies to treat the underlying cause can be prescribed. This statement provides a formal and updated definition for the broadly labelled term *MINOCA* (incorporating the definition of acute myocardial infarction from the newly released "Fourth Universal Definition of Myocardial Infarction") and provides a clinically useful framework and algorithms for the diagnostic evaluation and management of patients with myocardial infarction in the absence of obstructive coronary artery disease.

Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) was first documented >75 years ago when autopsy reports detailed myocardial necrosis in the absence of significant coronary atherosclerosis.[1,2] The pioneering angiographic studies by DeWood et al[3,4] reported a prevalence of nonobstructive coronary artery disease (CAD) in ≈5% of patients with acute myocardial infarction (AMI). This figure was subsequently confirmed in several large AMI registries[5] and in a large meta-analysis in which 6% of AMIs occurred in the absence of obstructive CAD.[6]

The term *MINC*[7] or *MINCA*[8] (myocardial infarction with normal coronary arteries) was initially coined to describe these patients and later evolved to *MINOCA*[9] to encompass patients with evidence of atherosclerosis that is not considered sufficiently severe to compromise myocardial blood flow. Accordingly, MINOCA is initially considered at the time of angiography as a working diagnosis until further assessment excludes other possible causes for troponin elevation. The management of patients with MINOCA will vary depending on the underlying cause, for which an extensive evaluation should be undertaken in all patients.

Unfortunately, despite many reviews[10,11] and a contemporary position statement from the European Society of Cardiology,[12] some clinicians still suppose that the absence of obstructive CAD excludes the possibility of an AMI. Great variability exists in the manner in which patients with suspected MINOCA are evaluated and treated. The extent of the diagnostic and therapeutic strategies implemented often depends on local nonstandardized practices and varies according to hospital resources. Furthermore, there is no clear consensus in the medical community about how best to

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address situations in which local resources do not permit more advanced diagnostic testing. Finally, there is limited agreement regarding the long-term medical management of patients with MINOCA.

The purpose of this statement is to provide a formal and updated definition for the broadly labelled term *MINOCA* (incorporating the definition of AMI from the newly released "Fourth Universal Definition of Myocardial Infarction"[13]) and to provide a clinically useful framework and algorithms pertaining to the diagnostic evaluation and management of these patients.

EPIDEMIOLOGY

Clinical studies have reported a prevalence of MINOCA of 5% to 6% of AMI cases,[6] with a range between 5% and 15% depending on the population examined.[5,6,14–16] Although MINOCA can present with or without ST-segment elevation on the ECG, patients with MINOCA are less likely to have electrocardiographic ST-segment deviations and have smaller degrees of troponin elevation than their AMI counterparts with obstructive CAD (AMI-CAD).[14,16]

The demographic and clinical characteristics of MINOCA patients differ from other patients with AMI. MINOCA patients are usually younger[6,14–16] than patients with AMI-CAD. In a large systematic review, the average age of patients with MINOCA was 58 years, compared with 61 years among those with AMI-CAD.[6] Women are disproportionately represented among individuals with MINOCA[5,6,14–18]; they make up close to 50% of the MINOCA population but only 25% of the population with AMI-CAD.[6] Women presenting with AMI are more than twice as likely as men to have MINOCA, whereas men presenting with AMI are more likely than women to have AMI-CAD.[5,6,14,15,17,18] MINOCA is also more likely to occur in patients of black, Maori, or Pacific race and Hispanic ethnicity.[5,14,16]

The prevalence of traditional CAD risk factors and clinical features also varies among patients with MINOCA versus AMI-CAD. MINOCA patients have a lower prevalence of dyslipidemia than their counterparts with AMI-CAD.[6,14,16,18] Other traditional CAD risk factors, such as hypertension, diabetes mellitus, tobacco abuse, and a family history of myocardial infarction, are less frequent in MINOCA patients,[14,16,18] although this has not been consistently observed in all studies.[6]

DEFINITIONS

Key Issues in Defining MINOCA

The rationale for defining MINOCA as a distinct entity is based on key clinical observations and premises, including the following: (1) Patients with MINOCA generally have a better prognosis than patients with AMI-CAD[6]; (2) multiple atherosclerotic and nonatherosclerotic causes with heterogenous pathophysiological mechanisms can cause MINOCA[12,16]; and (3) unlike AMI-CAD, there is a paucity of dedicated studies examining MINOCA and therefore a lack of evidence-based therapies in these patients.[12] Given the aforementioned suppositions, standardization of the definition of MINOCA is clinically pragmatic, has operational utility, and serves a key purpose in promoting clinical awareness and research into the condition.

The European Society of Cardiology[12] developed the first international position article on MINOCA and proposed the following MINOCA criteria: (1) AMI criteria as defined by the "Third Universal Definition of Myocardial Infarction"[19]; (2) nonobstructive coronary arteries as per angiographic guidelines,[20] with no lesions ≥50% in a major epicardial vessel; and (3) no other clinically overt specific cause that can serve an alternative cause for the acute presentation. Fundamental to the definition of MINOCA is the diagnosis of AMI with an elevated cardiac biomarker, typically a cardiac troponin >99th percentile of the upper reference level with a rise or fall in the level on serial assessment. Although elevated troponin levels are indicative of myocyte injury with release of this intracellular protein into the systemic circulation, the process is not disease specific and can result from either ischemic or nonischemic mechanisms. Given this limitation of the troponin bioassay, the "Fourth Universal Definition of Myocardial Infarction" (by the Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction) recently redefined the concept of myocardial injury.[13] Similar to myocardial infarction, the hallmark of myocardial injury is an elevated troponin beyond the 99th percentile of the upper reference level. However, these entities differ conceptually, because myocardial injury is attributable to nonischemic mechanisms of myocyte injury (eg, myocarditis), whereas myocardial infarction arises from ischemic mechanisms (eg, plaque disruption or supply-demand mismatch). The clinical diagnostic challenge is to delineate these entities, because patients with myocardial injury can present with symptoms that mimic myocardial infarction at the initial presentation.

With this revised concept of AMI, the term *MINOCA* should be reserved for patients in whom there is an ischemic basis for their clinical presentation. Thus, in the evaluation of patients with a suspected AMI (based on cardiac biomarkers and corroborative clinical evidence), despite the absence of obstructive CAD, it is imperative to exclude (1) clinically overt causes for the elevated troponin (eg, sepsis, pulmonary embolism), (2) clinically overlooked obstructive disease (eg, complete occlusion of a small coronary artery subsegment resulting from plaque

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disruption or embolism, or an overlooked ≥50% distal stenosis of a coronary artery), and (3) clinically subtle nonischemic mechanisms of myocyte injury that can mimic myocardial infarction (eg, myocarditis) (Figure 1). Once these have been considered and excluded by use of available diagnostic resources, a diagnosis of MINOCA can be made (Table 1). This diagnosis is inherently descriptive and should prompt physicians to seek an underlying diagnosis.

The angiographic 50% threshold definition for obstructive disease is somewhat arbitrary but both pragmatic and consistent with previous American Heart Association/American College of Cardiology coronary angiography guidelines.[20] Although an obstructive lesion is strictly a pathophysiological concept that requires physiological evaluation, functional assessment is not routinely undertaken in all patients undergoing coronary angiography, and clinical decisions are often made on the basis of visual angiographic estimation of lesion diameter stenosis. Yet it is important to realize that this approach to classification of lesion severity is extremely subjective, with substantial interobserver variability.[21] Furthermore, the angiographic severity of a lesion is not static and can vary between angiograms as a result of changes in vasomotor tone or dissolution of coronary thrombi.[22] In accordance with this pragmatic angiographic approach, it is useful to categorize MINOCA patients into those with angiographically normal coronary arteries (ie, no angiographic disease) and minimal lumen irregularities (angiographic disease <30% stenosis) and those with angiographically mild to moderate coronary atherosclerosis (≥30% but <50%). This somewhat arbitrary delineation is supported by earlier data suggesting that patients with a larger atherosclerotic burden on angiography have a poorer prognosis.[23] Although there are limited data evaluating the role of fractional flow reserve (FFR) testing in MINOCA patients with moderate stenoses, FFR may be considered in select patients with borderline "obstructive" disease based on extrapolation from data in stable patients that showed that up to one-quarter of patients with 30% to 50% stenosis have functionally significant stenoses when measured using FFR.[24] If FFR is used, we propose that only patients with FFR findings >0.80 be included as a working diagnosis of MINOCA.

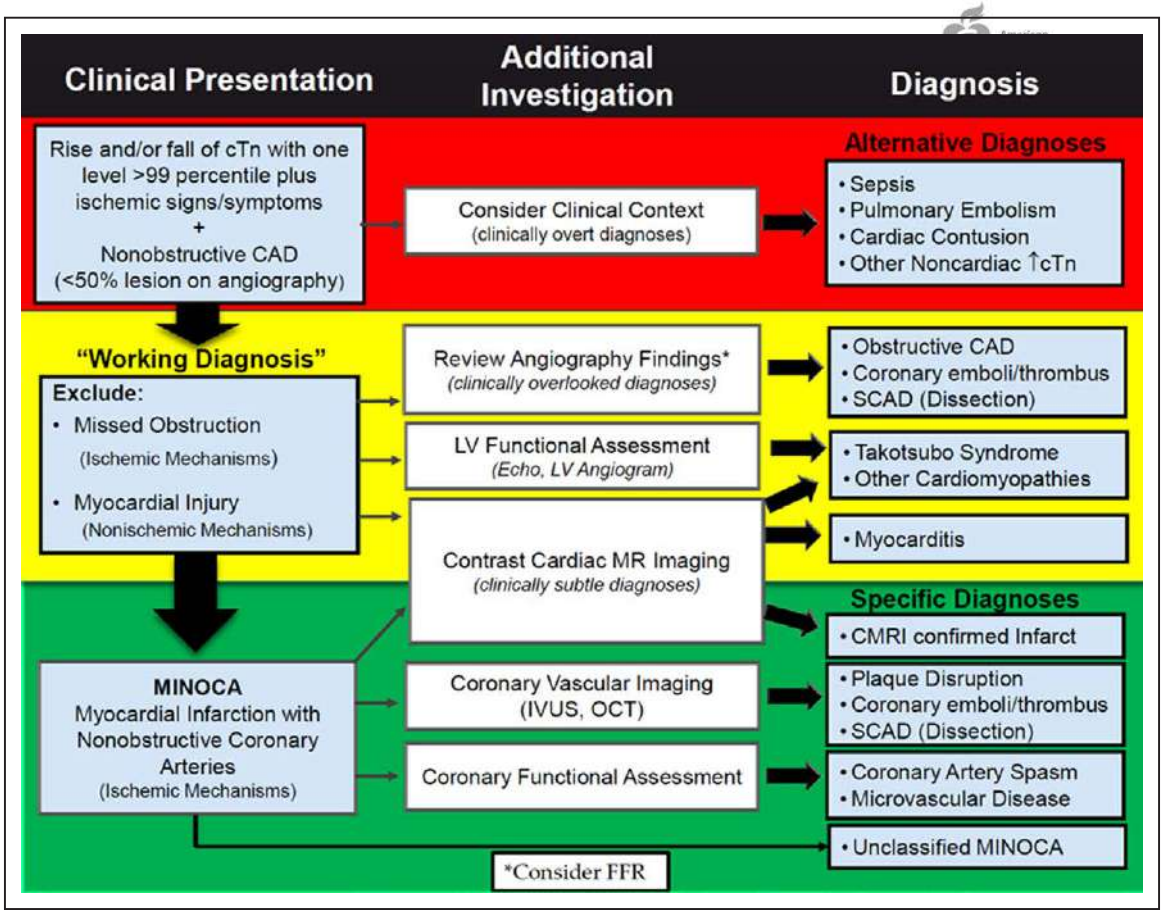

Figure 1. Clinical algorithm for the diagnosis of MINOCA.
CAD indicates coronary artery disease; CMRI, cardiac magnetic resonance imaging; cTn, cardiac troponin; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LV, left ventricular; MINOCA, myocardial infarction in the absence of obstructive coronary artery disease; MR, magnetic resonance; OCT, optical coherence tomography; and SCAD, spontaneous coronary artery dissection.
*Consider FFR.

Table 1. MINOCA Diagnostic Criteria

The diagnosis of MINOCA is made in patients with acute myocardial infarction that fulfills the following criteria:
1. Acute myocardial infarction (modified from the "Fourth Universal Definition of Myocardial Infarction" Criteria)
Detection of a rise or fall of cTn with at least 1 value above the 99th percentile upper reference limit
and
Corroborative clinical evidence of infarction evidenced by at least 1 of the following:
Symptoms of myocardial ischemia
New ischemic electrocardiographic changes
Development of pathological Q waves
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic cause
Identification of a coronary thrombus by angiography or autopsy
2. Nonobstructive coronary arteries on angiography:
Defined as the absence of obstructive disease on angiography (ie, no coronary artery stenosis ≥50%) in any major epicardial vessel*
This includes patients with:
Normal coronary arteries (no angiographic stenosis)
Mild luminal irregularities (angiographic stenosis <30% stenoses)
Moderate coronary atherosclerotic lesions (stenoses >30% but <50%)
3. No specific alternate diagnosis for the clinical presentation:
Alternate diagnoses include but are not limited to nonischemic causes such as sepsis, pulmonary embolism, and myocarditis

cTn indicates cardiac troponin; and MINOCA, myocardial infarction in the absence of obstructive coronary artery disease.

*Note that additional review of the angiogram may be required to ensure the absence of obstructive disease.

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The "Traffic Light" Sequence for the Diagnosis of MINOCA

Figure 1 provides a clinical algorithm for the diagnosis of MINOCA. The initial evaluation in patients with suspected AMI and nonobstructive CAD involves careful consideration of the clinical context and the exclusion of clinically overt causes for a myocardial injury that led physicians to an initial diagnosis of AMI but on further review was not likely a result of an ischemic event (red section of Figure 1). If AMI remains the clinical diagnosis of choice after this step, the clinician should exclude potentially overlooked obstructive CAD by re-reviewing the angiogram and consider further investigation to exclude clinically subtle nonischemic mechanisms of myocardial injury (yellow section of Figure 1). Cardiac magnetic resonance imaging (CMRI) is recommended as a key investigation in MINOCA because it can exclude myocarditis, takotsubo syndrome, and cardiomyopathies, as well as provide imaging confirmation of AMI. However, CMRI is not widely available, and it is therefore not pragmatic to recommend it as an essential step for the diagnosis of MINOCA. After excluding alternate diagnoses, the clinician arrives in the green section of Figure 1, where a diagnosis of MINOCA or CMRI-confirmed MINOCA can be made. In specialized centers, the clinician may consider additional studies to elucidate the underlying cause(s) of MINOCA. It is important to recognize that the order of the diagnostic evaluations advised might not always follow the algorithm provided. For example, CMRI might be performed after intracoronary imaging.

Several aspects of this working-diagnosis pathway are noteworthy:

- Clinically overt presentation: The initial presentation might provide an obvious clinical context for the diagnosis (eg, myocardial injury associated with septic shock) that would not be considered MINOCA, so that no further diagnostic evaluation is required.
- Access to cardiac investigations: Some cardiac investigations (eg, CMRI) might not be readily available in some centers, so that the diagnosis of MINOCA may need to be made on clinical grounds alone. However, consideration should be given to these alternate diagnoses even in the absence of advanced imaging. Notably, although the use of CMRI is strongly encouraged, the absence of myocardial necrosis on CMRI does not necessarily exclude MINOCA as a diagnosis, because a lack of myocardial necrosis on CMRI has been reported in patients with other findings that support MINOCA.[25]
- Dynamic diagnosis: With further evaluation, the differential clinical diagnoses may change. For example, an initial diagnosis suggestive of takotsubo syndrome based on left ventricular imaging studies may later change to MINOCA if CMRI demonstrates myocardial necrosis. Similarly, an initial diagnosis of MINOCA may later change to myocarditis on the basis of CMRI findings.
- Takotsubo syndrome: The mechanism (ischemic versus nonischemic) responsible for this intriguing disorder remains uncertain. Criteria for takotsubo syndrome require the wall motion abnormalities to be transient, and therefore, early in the course, the working diagnosis might be MINOCA. The "Fourth Universal Definition of Myocardial Infarction" does not consider takotsubo syndrome a myocardial infarction,[13] and therefore, we have categorized takotsubo syndrome separately for uniformity. Although takotsubo syndrome can clinically mimic MINOCA, it appears to be a distinctly different syndrome and therefore should be considered separately.
- Evaluating ischemic mechanisms: Invasive coronary imaging and functional testing can provide

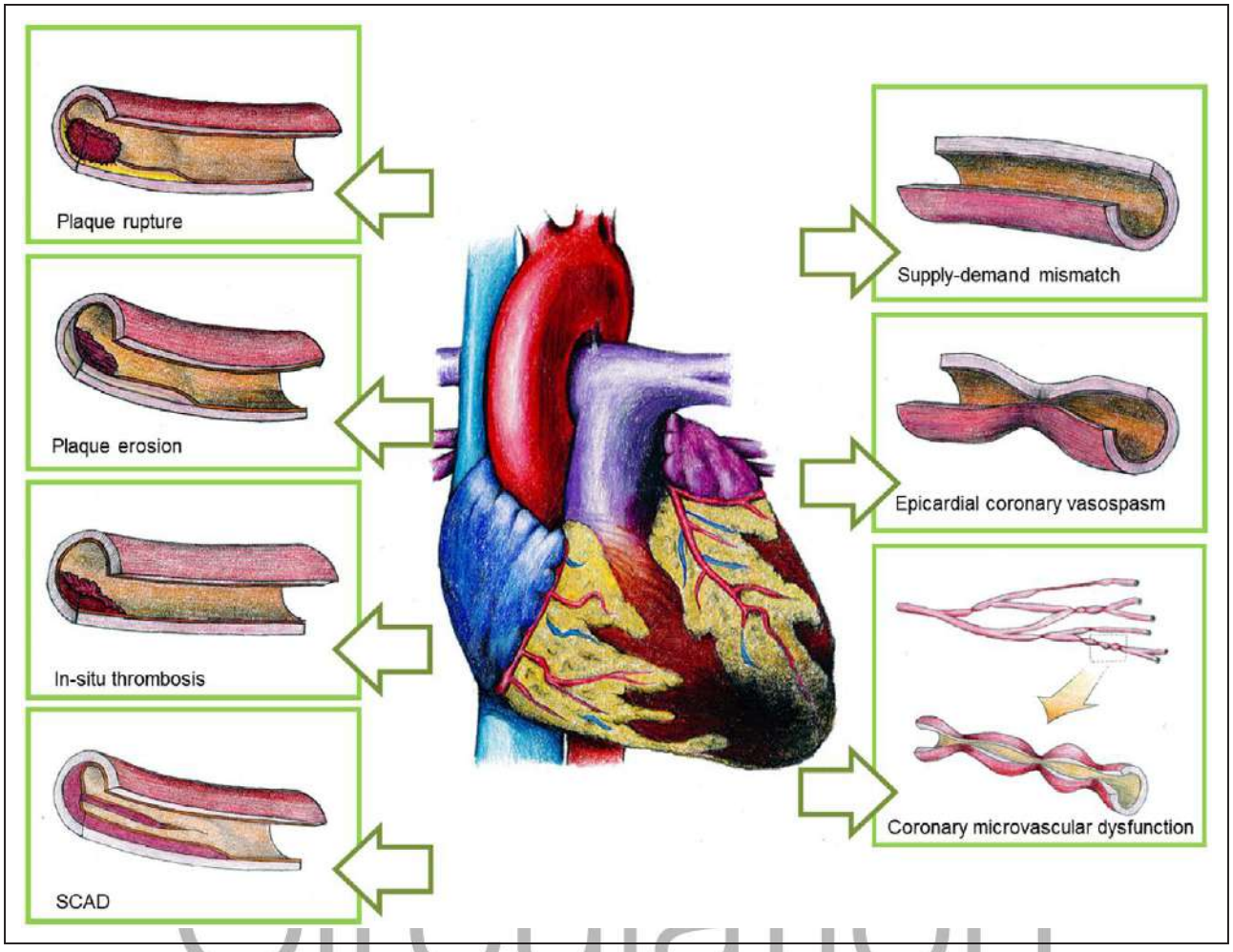

Figure 2. Specific causes.
SCAD indicates spontaneous coronary artery dissection.

therapeutic direction for patients with MINOCA (eg, use of calcium channel blockers in coronary spasm) and should be used selectively after consideration of the benefits and risks.

- Spontaneous coronary artery dissection (SCAD): The diagnosis of SCAD is usually made after careful review of the angiogram. If obstructive disease is noted, this would eliminate a diagnosis of MINOCA. However, on occasion, SCAD is only recognized after intracoronary imaging is performed, and hence, imaging may be needed to firmly establish the diagnosis, especially in SCAD subtype II (diffuse long, smooth, tapering nonobstructive lesions).[26]

SPECIFIC CAUSES

Atherosclerotic Causes of Myocardial Necrosis

Plaque Disruption

Coronary plaque disruption is common among MINOCA patients (Figure 2). The term *plaque disruption* encompasses plaque rupture, plaque erosion, and calcific nodules. Plaque disruption can trigger thrombus formation that leads to AMI via distal embolization, superimposed coronary spasm, or perhaps, in some cases, transient complete thrombosis with spontaneous thrombolysis. The angiographic appearance may suggest plaque disruption; for example, haziness or a small filling defect. Plaque disruption can only be definitively diagnosed with intracoronary imaging, preferably with the higher-resolution optical coherence tomography (OCT) imaging or, to a lesser extent, with intravascular ultrasound (IVUS). Coronary computed tomography angiography does not provide sufficient detail of the luminal interface. Plaque rupture is defined as fibrous cap discontinuity leading to a communication between plaque cavity and the coronary lumen. Compared with plaque erosion, plaque rupture is associated with a higher frequency of thin-cap fibroatheroma and disruption in nonculprit lesions[27] or non–infarct-related arteries. Plaque erosion is defined as a thrombus contiguous to the luminal surface of a plaque without signs of rupture.[27] Plaque erosion is a distinct entity caused primarily

by endothelial erosion, compared with plaque rupture caused by inflammation.[28] The mechanisms underlying plaque erosion are currently poorly defined but appear to be related to apoptosis of endothelial cells and loss of endothelial contact with the underlying extracellular matrix[29]; this process can be promoted by several triggers, such as coronary spasm.[30] On pathological evaluation of sudden death cases, plaque erosion was associated with more late-stage thrombus (versus early, <1-day-old thrombus for plaque rupture)[31] and more frequent distal embolization.[32] Plaque erosion could have an important pathophysiological role in MINOCA patients, because angiographic evidence of obstruction in major epicardial vessels is not evident in these patients, and the myonecrosis may result from distal embolization. Calcified nodule is defined based on OCT imaging criteria as a signal-poor region with poorly delineated borders that protrudes into the arterial lumen; it is the least common cause of plaque disruption and is more common in older patients.[33]

Plaque disruption is noted on IVUS in approximately one-third of patients with MINOCA.[25,34] Reynolds et al[25] reported plaque disruption using IVUS in 16 of 42 women with MINOCA (38%); plaque rupture was present in 11 patients, plaque ulceration (a crater in plaque not meeting criteria for rupture) in 4 patients, and both plaque rupture and ulceration in 1 patient. Some patients had multiple ruptured plaques, as has been observed in patients with AMI-CAD.[35] Ouldzein et al[34] found a 37% rate of plaque rupture in a cohort of 68 patients with MINOCA. The prevalence of plaque disruption might be even higher than previously reported if higher-resolution imaging (eg, OCT) is used, particularly given that plaque erosion is not detected by IVUS.[36] Furthermore, in the aforementioned studies, imaging was performed on 1 or 2 coronary arteries rather than all 3 arteries, and identification of the AMI culprit vessel on angiography can be particularly challenging in MINOCA patients. Plaque disruption was located in a vessel segment that appeared angiographically normal in nearly half of the cases with rupture or ulceration, although all patients with plaque disruption had evidence of at least minor atherosclerosis somewhere on the angiogram.[37] The frequency of plaque erosion in MINOCA has not been established, because published studies have used IVUS rather than OCT. This entity has been observed in MINOCA patients by the authors, and it is likely that plaque erosion is a common cause of MINOCA, as it is in patients with AMI-CAD.[38] Plaque erosion is more common in women, smokers, patients with single-vessel disease, and younger patients with few risk factors for CAD.[29] Plaque erosion is also more common among young women who died suddenly in pathological series of sudden cardiac death, which is interesting given the predilection of MINOCA for younger patients and women.[39] MINOCA with calcified nodule has been reported but seems to be rare.[33]

To date, plaque rupture and erosion have only been reported among patients with MINOCA with some evidence of atherosclerosis on angiography; for instance, luminal irregularities or plaque causing <50% stenosis. Given the frequent presence of plaque disruption in patients with MINOCA undergoing invasive imaging studies, the authors recommend that if available, OCT or IVUS imaging be performed in patients with MINOCA and evidence of nonobstructive atherosclerosis on an angiogram. OCT has better resolution and is the preferable modality.

Nonatherosclerotic Causes of Myocardial Necrosis

Epicardial Coronary Vasospasm

Coronary artery spasm is defined as intense vasoconstriction (ie, >90%) of an epicardial coronary artery resulting in compromised myocardial blood flow. Coronary vasospasm can occur either in response to drugs or toxins (eg, cocaine, fluorouracil) that result in hyperreactivity of vascular smooth muscles or spontaneously because of disorders in coronary vasomotor tone. Vasospastic angina is a clinical disorder manifesting as rest angina associated with a dynamic ST-segment elevation pattern on ECG as a result of coronary artery spasm.[40] Although the disorder was first described by Prinzmetal et al[41] in patients with obstructive CAD, it is more often considered in patients with nonobstructive coronaries. Prolonged vasospastic episodes can also result in MINOCA. Vascular smooth muscle hyperreactivity appears to be a central pathophysiological mechanism, with the relative roles of the endothelial and adventitial layers in modulating this hyperreactivity (particularly in relation to inflammatory mechanisms) rapidly evolving.[42]

Coronary vasospasm is a common cause of MINOCA. In one study, coronary vasospasm was diagnosed in 46% of patients with MINOCA undergoing provocative testing.[43] There is a predilection for vasospastic angina among Asian patients compared with whites.[6,44] Among patients with MINOCA, postdischarge (up to 6 weeks after AMI) provocative testing for vasospasm suggests a higher prevalence of vasospastic angina in Japanese (81%) and Korean (61%) patients than in whites (15%).[6]

The diagnosis of vasospastic angina typically requires the documentation of coronary artery spasm. Although spontaneous episodes may be fortuitously documented,[40] provocative spasm testing is often required to establish the diagnosis. Over the years, a number of coronary spasm provocation testing methods have been developed, but the gold standard technique involves administration of high-dose intracoronary acetylcholine boluses (20-100 μg administered as an intracoronary 5-mL bolus over 20 seconds), with the epicardial coronary artery response evaluated by invasive contrast an-

giography.[45] This method has been validated in patients with spontaneous episodes of spasm[45] and widely used in Japanese and Korean clinical practices but has been restricted to specialized centers in Europe and the United States.

European and US centers have been reluctant to perform routine provocative testing after reported deaths occurring in the 1970s with ergonovine provocative testing.[46] These were undertaken as bedside tests with often intermittent electrocardiographic monitoring alone, with sublingual nitrate as the principal treatment for any induced spasm. This contrasts with contemporary catheterization laboratory–based provocative testing during which acetylcholine is used (very short half-life), spasm is documented angiographically (ie, before significant ischemic electrocardiographic changes), and intracoronary nitrates are rapidly administered. With this contemporary approach, large spasm registries have reported an acceptable level of safety in provocative testing of stable patients, with no reported procedure-related deaths, although significant bradyarrhythmias or tachyarrhythmias were induced in up to 6% of patients.[47,48] This is comparable to the prevalence of arrhythmias reported during spontaneous episodes of spasm,[47,48] which suggests the arrhythmias were a result of the vasospastic episode rather than the provocative testing itself. However, until recently, spasm provocative testing was seldom performed in MINOCA patients during their index admission. Montone et al[43] reported the first safety data for early provocative spasm testing in a study of 80 patients with MINOCA undergoing provocative spasm testing within 48 hours of admission. Provocative spasm testing revealed positive results in 37 patients (46.2%). Procedure-related arrhythmias occurred in 5% of patients, and no major adverse events, including death or recurrent infarction, were reported.

Coronary Microvascular Dysfunction

Although the epicardial coronary arteries are easily visualized via coronary angiography and amenable to revascularization therapies, the coronary microcirculation (vessels <0.5 mm diameter) is not easily visualized yet accounts for ≈70% of the coronary resistance in the absence of obstructive CAD.[49] Microvascular dysfunction can potentially contribute to the pathogenesis of MINOCA and is divided into endothelium-dependent or -independent dysfunction.

Clinical disorders of coronary microvascular dysfunction have largely been described in patients presenting with stable angina.[50] A standardized definition for microvascular angina has been established and includes patients with ischemic chest discomfort, nonobstructive coronary arteries, and an impaired coronary flow.[51] Impaired coronary flow can be determined by any of the following: (1) coronary flow reserve <2.0 in response to vasodilator stimuli such as adenosine[51]; (2) evidence of microvascular spasm diagnosed during provocative spasm testing, when chest discomfort and ischemic electrocardiographic changes are induced by acetylcholine provocation in the absence of epicardial coronary spasm[48]; or (3) impaired coronary blood flow, as measured with a corrected TIMI (Thrombolysis in Myocardial Infarction) frame count. (This is also known as the *coronary slow flow phenomenon*, an angiographic phenomenon that can occur spontaneously and is characterized as a delayed passage of angiographic contrast [requiring ≥3 beats to fill a vessel] at rest.) Coronary hemodynamic studies have shown increased basal microvascular resistance in patients with coronary slow flow phenomenon.[52] In clinical practice, combined assessment of epicardial spasm and microvascular disease might be most practical using combined testing, where available.

Coronary microvascular dysfunction can be detected in 30% to 50% of patients with chest discomfort and nonobstructive CAD on invasive coronary angiography.[51] It is more commonly seen in women and patients with cardiovascular risk factors (eg, increasing age, diabetes mellitus, hypertension, smoking, or dyslipidemia).[50] MINOCA is distinct from ischemia with nonobstructive CAD; the latter occurs in stable patients who do not have myocardial infarction.[50] There is limited overlap between MINOCA and ischemia with nonobstructive CAD. For example, among patients with microvascular coronary disease, few are found to have evidence of prior AMI; only 26 of 340 women (8%) with stable microvascular disease undergoing CMRI in the WISE study (Women's Ischemia Syndrome Evaluation) had magnetic resonance imaging evidence of myocardial scar.[53]

Microvascular dysfunction can be a cause of ischemia but can also be a sequela of myocardial injury of an ischemic or nonischemic origin. For example, a stress cardiac magnetic resonance study of 40 female patients with MINOCA reported that two-thirds of patients had an inducible perfusion abnormality,[54] which implies the presence of coronary microvascular dysfunction. However, stress perfusion abnormalities were seen in patients with any reason for myocardial edema, including myocarditis. Thus, the challenge to identifying the role of microvascular dysfunction in MINOCA is to determine whether it is a cause of the AMI or a consequence of it. Although invasive assessment for microvascular dysfunction can be considered in patients with MINOCA, it might not conclusively delineate the reason for the acute presentation. Therefore, the role of coronary microvascular dysfunction in MINOCA requires further investigation, with limited studies evaluating the roles of microvascular angina, microvascular spasm, or the coronary slow flow phenomenon in these patients.

Coronary Embolism/Thrombosis

Coronary thrombosis or embolism results in MINOCA if it involves the microcirculation or if partial lysis of the

epicardial coronary thrombus results in nonobstructive angiographic disease. This can occur with or without a hypercoagulable state.

Hypercoagulable disorders that result in coronary thrombosis can be divided into inherited and acquired causes. Inherited thrombophilia is prevalent in the general population (eg, factor V Leiden [in 5%], elevated factor VIII/von Willebrand factor [in 25%]), with varying prevalence by race/ethnicity.[55] Acquired hypercoagulable states include thrombotic thrombocytopenic purpura (TTP), the autoimmune disorder antiphospholipid syndrome, heparin-induced thrombocytopenia (HIT), and myeloproliferative neoplasms. In a systematic review examining the use of thrombophilia testing in MINOCA patients,[6] factor V Leiden or activated protein C resistance followed by protein C or S deficiency was most commonly observed (in 12% and 3% of patients, respectively). It is reasonable to consider the inherited hypercoagulable states in patients with MINOCA, especially in younger women.[56–62] A case-control study of 362 young women reported an odds ratio of AMI of 3.7 associated with factor V Leiden and an odds ratio of 3.8 for the prothrombin 20120A,[57] whereas another study including 1670 men and 210 women with AMI <45 years of age suggested lower risks of 1.7 and 1.3, respectively.[63] It is important that testing for coagulation factor levels be performed after the acute-phase illness has resolved and that patients be aware of the strengths and limitations of testing and understand its implications for family members.[64] Diagnostic testing for inherited coagulopathies in patients with suspected MINOCA is preferably performed in consultation with a hematologist and can include several tests (eg, factor V Leiden, prothrombin 20210A, factor VIII, protein C activity, protein S activity, antithrombin, lupus anticoagulant, and a comprehensive panel for antiphospholipid antibodies).

TTP is a thrombotic microangiopathy characterized by microangiopathic hemolytic anemia and profound thrombocytopenia[65] and is an infrequent cause of MINOCA.[66] It should be suspected in cases of AMI occurring together with thrombocytopenia and hemolytic anemia, when there are schistocytes on the peripheral smear. A report from the Nationwide Inpatient Sample (2007–2012) inclusive of 8203 TTP hospitalizations reported an AMI rate of 5.6% in patients with TTP, but it is unclear how many of those fit the MINOCA definition.[67]

Antiphospholipid syndrome is a heterogenous disorder characterized by autoantibodies against protein-phospholipid complexes that promote a hypercoagulable state. The diagnosis requires presence of thrombosis or pregnancy complications along with characteristic laboratory abnormalities (lupus anticoagulant or serological tests for antiphospholipid antibodies).[68] Laboratory abnormalities must be persistently present at least 12 weeks apart, because transient abnormalities are not clinically significant. Venous thrombosis is a more common presentation, and among those presenting with arterial thrombosis, stroke is 4 times more common than AMI (which occurs in ≈5% of patients).[69] Among patients with coronary embolism, one study reported 7.5% had antiphospholipid syndrome.[70]

HIT occurs when antibodies develop against heparin-platelet factor 4 complexes. It is more common after exposure to unfractionated heparin than to low-molecular-weight heparin and can result in an intense hypercoagulable state accompanied by venous or arterial thrombosis, especially in recently instrumented vessels.[71] The platelet count is not always low in HIT and is rarely severely low; diagnostic criteria for HIT require a decline to <50% of the pre-heparin count, so not all patients are thrombocytopenic.

Myeloproliferative neoplasms, such as polycythemia vera and essential thrombocythemia, are rare clonal hematologic diseases that have venous or arterial thrombosis as common manifestations.

Spontaneous Coronary Artery Dissection

SCAD is a relatively uncommon nonatherosclerotic mechanism of AMI; however, it is a common cause of AMI among women <50 years of age.[72–74] Although most patients with SCAD have some obstruction to flow, occasionally the arteries can appear normal or near normal because of gradual tapering of the vessel, and hence, this should be considered as a possible cause for MINOCA. It remains possible that with greater use of intracoronary imaging, SCAD that is not angiographically obstructive will increasingly be recognized as a cause of MINOCA.

The obstruction to coronary blood flow in SCAD is generated by a separation of the media and adventitial vascular walls associated with intramural hematoma protrusion into the lumen. It can occur in single or multiple coronary vessels. The exact mechanism of SCAD is not entirely known, and the primary source of the dissection (intimal or medial) is still controversial. SCAD might represent an intrinsic underlying vasculopathy that could be compounded by a precipitating stressor associated with a catecholamine surge, such as emotional stress, extreme physical activities, and sympathomimetic drugs.[75] The strong association between SCAD and other vascular diseases (eg, fibromuscular dysplasia) supports this theory.[73] Initial reports linked the incidence of SCAD to pregnancy, in which SCAD was found to occur antepartum, early postpartum, and late postpartum.[76]

The exact incidence of SCAD is controversial, because many events can be missed or misdiagnosed.[77] SCAD was initially estimated to occur in ≈1% of patients with acute coronary syndromes, but a more accurate estimate of its prevalence in patients with acute

coronary syndromes may be higher, in the range of 1.7% to 4%. Within a population of women <50 years of age presenting with acute coronary syndrome, the prevalence of SCAD could be up to 35%.[73,77,78] For all the aforementioned reasons, it is difficult to accurately determine the incidence of SCAD in patients with MINOCA.

SCAD should be suspected mainly in young women presenting with acute coronary syndrome or sudden cardiac death. The angiographic appearance can vary from a near-normal coronary artery to arterial wall contrast staining with multiple radiolucent lumens or diffuse stenosis of varying severity, including <50% stenosis.[79] The appearance of tortuosity, including corkscrew appearance and multivessel symmetrical tortuosity, is also characteristic of SCAD.[80] However, a definitive diagnosis can require intravascular imaging such as IVUS or OCT demonstrating the lack of significant atherosclerotic plaque and the presence of dissection and intramural hematoma. Because of the superior resolution of OCT, OCT is the preferred imaging modality when evaluating a patient with suspected SCAD,[78] although care must be taken to avoid the possibility of contrast-induced hydraulic extension of the dissection during OCT imaging.

Supply-Demand Mismatch

The "Fourth Universal Definition of Myocardial Infarction" (2018)[13] describes type 2 myocardial infarction events as those secondary to an ischemic imbalance. This is a heterogeneous category that includes many of the pathophysiological mechanisms mentioned previously (eg, coronary spasm, thrombosis) and other systemic conditions resulting in supply-demand mismatch (eg, tachyarrhythmias, anemia, hypotension, thyrotoxicosis). Several studies have shown variability in the categorization of myocardial infarction events as type 1 or type 2,[81,82] which in part reflects the moderate agreement (at best) among trained clinicians when classifying AMI types.[83] This variability was further evident if the classification extended beyond those with obstructive CAD.[84] The diagnosis of a type 2 myocardial infarction, as opposed to myocardial injury, requires other corroborating evidence (Table 1), including ischemic symptoms or signs and a rise or fall in troponin levels. The presence of CAD is not necessary for the diagnosis. This diagnosis should not be liberally given to all patients with an elevated troponin level in the setting of hypotension or tachycardia without other findings to suggest myocardial ischemia. Tachyarrhythmia-associated AMI is one of the common causes of type- 2 myocardial infarction,[82,83] although sometimes it is difficult to distinguish whether the tachyarrhythmia is a cause or a consequence of the MINOCA event in a particular patient. In general, the diagnosis of a type 2 myocardial infarction in patients with MINOCA is made when a plausible cause exists (eg, tachycardia, anemia, hypotension) in the absence of clinical, angiographic, or invasive imaging modalities that would otherwise support a different diagnosis.

MANAGEMENT STRATEGIES

The management of AMI with obstructive CAD is well established, with detailed evidence-based guidelines for both ST-segment–elevation myocardial infarction[85] and non–ST-segment–elevation myocardial infarction.[86] In contrast, the management of MINOCA has a limited evidence-based literature, with no prospective randomized, controlled trials undertaken to date. Given these therapeutic shortcomings, it is important to define the management strategy for patients with MINOCA, which includes careful consideration of the following: (1) emergency supportive care; (2) a working diagnosis approach for patient evaluation; (3) cardioprotective therapies irrespective of the cause of the MINOCA; and (4) cause-targeted therapies.

Emergency Supportive Care

An important number of MINOCA patients can require emergency therapies for life-threatening arrhythmias or cardiogenic shock. Although revascularization is a cornerstone therapy for AMI-CAD, it is not a therapeutic option in patients with MINOCA. Therefore, the astute clinician must always consider the possible causes for MINOCA, especially in the initial setting, and immediately address the underlying mechanism responsible for a patient's compromised condition. For example, in the case of ventricular arrhythmias as a result of refractory spasm, coronary vasodilator drugs are the treatment of choice and should be initiated promptly.

MINOCA: A Working Diagnosis

It is imperative that the diagnosis of MINOCA be considered as a working diagnosis to elucidate the underlying cause of the clinical presentation. This needs to be undertaken at 2 levels, to (1) exclude disorders mimicking an AMI and (2) identify the underlying cause responsible for the MINOCA. Table 2 summarizes the extensive array of specific therapies that must be considered in patients suspected of having MINOCA.

Cardioprotective Therapies

All patients with AMI-CAD (ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction) require secondary prevention therapies. These include conventional cardioprotective medications

Table 2. Management of Patients With a Working Diagnosis of MINOCA

Underlying Mechanism/Clinical Disorder	Selective Diagnostic Investigations*	Selective/Empirical Therapies†
Clinically overlooked ischemic or nonischemic presentations (mimicking MINOCA)		
Branch "flush occlusion" or severe branch stenosis (from coronary embolism/thrombus or ruptured plaque)	Angiographic review Consider intracoronary imaging to identify plaque rupture or dissection, or de novo thrombus echocardiography review (screen valves for endocarditis; left atrium and left ventricle for thrombus source and tumor; the possibility of a PFO should also be evaluated)	Antiplatelet or anticoagulant (depending on cause) Statin β-blockers ACE inhibitors/ARBs (in presence of left ventricular dysfunction, and possibly with preserved EF)
Spontaneous coronary artery dissection	Angiographic review	Aspirin β-blocker Consider clopidogrel
Takotsubo syndrome	Left ventricular angiogram Contrast CMRI	ACE inhibition Medical or device therapies for heart failure/left ventricular dysfunction Consider β-blockers
Cardiomyopathies	Contrast CMRI	Medical or device therapies for heart failure/left ventricular dysfunction
Myocarditis	Contrast CMRI	Medical or device therapies for heart failure/left ventricular dysfunction. Consider immunomodulatory and immunosuppressive therapies
Ischemic presentation (MINOCA)		
Plaque disruption	Angiographic review Intravascular imaging (IVUS or OCT)	Aspirin High-intensity statin β-blockers (in presence of left ventricular dysfunction, and possibly with preserved EF) ACE inhibitors/ARBs (in presence of left ventricular dysfunction, and possibly with preserved EF) Consider clopidogrel/ticagrelor
Coronary artery spasm	Resolution with coronary vasodilators (eg, intracoronary nitroglycerin) Provocative spasm testing Blood toxicology testing Review of medication and nonprescription drug use (eg, migraine medications, cocaine)	Calcium channel blockers Other antispastic agents (nitrates, nicorandil, cilostazol) Consider statin
Coronary microvascular dysfunction	Angiographic review Coronary microvascular functional testing	Conventional antianginal therapies (eg, calcium channel blocker, β-blocker) Unconventional antianginal therapies (eg, L-arginine, ranolazine, dipyridamole, aminophylline, imipramine, α-blockers)
Coronary embolism/thrombus	Angiographic review Intravascular imaging (IVUS or OCT) Thrombophilia screen	Antiplatelet or anticoagulant therapy Other targeted therapies for hypercoagulable condition
Spontaneous coronary artery dissection	Angiographic review Intravascular imaging (IVUS or OCT)	Aspirin β-blocker Consider clopidogrel
Supply-demand mismatch	Review history for potential stressors	Treatment for underlying condition

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CMRI, cardiac magnetic resonance imaging; EF, ejection fraction; IVUS, intravascular ultrasound; MINOCA, myocardial infarction in the absence of obstructive coronary artery disease; OCT, optical coherence tomography; and PFO, patent foramen ovale.

*These are selective and targeted investigations and should be considered in addition to routine evaluation for patients with suspected acute myocardial infarction, including clinical assessment, ECG, cardiac biomarkers (with troponins preferred), and echocardiogram.

†These are selective and targeted therapies and should be considered in addition to cardioprotective therapies, lifestyle changes, and cardiac rehabilitation.

(dual antiplatelet agents, statins, angiotensin-converting enzyme [ACE] inhibitors /angiotensin receptor blockers [ARBs], and β-blockers), risk factor modification with nonpharmacological therapies, and cardiac rehabilitation. The secondary prevention therapies largely target the atherothrombotic process. In MINOCA patients, however, the atherosclerotic burden is reduced or minimal, which calls into question the value of routine use of

some of these therapies. These therapies should therefore be considered on an individual basis in patients with MINOCA. For example, antiplatelet therapy and statins are strongly recommended for MINOCA patients with plaque disruption (type 1 AMI), but their routine use in type 2 AMI is uncertain and may be contraindicated (eg, β-blockers in patients with coronary spasm).

To address this issue, Lindahl et al[15] undertook a stratified propensity analysis of 9138 patients with MINOCA enrolled in the SWEDEHEART registry (the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy), evaluating the relationship between treatment with (1) statins, (2) ACE inhibitors/ARBs, (3) β-blockers, and (4) dual antiplatelet therapy and the composite of all-cause mortality or hospitalization for reinfarction, heart failure, or stroke. After a mean follow-up of 4.1 years, there was a significantly lower event rate associated with the use of statins (hazard ratio, 0.77 [95% CI, 0.68–0.87]) and ACE inhibitors/ARBs (hazard ratio, 0.82 [95% CI, 0.73–0.93]) and a trend for a lower event rate with the use of β-blockers (hazard ratio, 0.86 [95% CI, 0.74–1.01]). The use of dual antiplatelet agents was not associated with a lower event rate (hazard ratio, 0.90 [95% CI, 0.74–1.08]). The results from this retrospective analysis provide some support for the use of cardioprotective therapies (except dual antiplatelet agents) in patients with MINOCA, although we await the results from randomized, controlled trial data before any strong recommendations can be made. The MINOCA BAT (Randomized Evaluation of Beta-Blocker and ACEI/ARB Treatment in MINOCA Patients) aims to randomize at least 3500 MINOCA patients to treatment with ACE inhibitors/ARBs and β-blockers or matching placebo. This study will examine all-cause mortality and cardiovascular events at 1 year and should provide us with important information regarding the benefits of routine cardioprotective therapies in MINOCA patients. Of note, in any MINOCA patient with any evidence of atherosclerosis, modifiable CAD risk factors (such as smoking, hypertension, diabetes mellitus, and hyperlipidemia) should be treated aggressively.

Cause-Targeted Therapies

Plaque Disruption

MINOCA patients who are determined to have plaque disruption should be prescribed cardioprotective therapies in accordance with the AMI guidelines,[15] with aspirin being the mainstay initial therapy because the pathogenesis is similar to that of AMI-CAD. Treatment should be identical for plaque rupture and plaque erosion, because no distinction is made between these 2 entities in current American Heart Association/American College of Cardiology AMI guidelines.[85,86] Although the observational cohort study of patients enrolled in the SWEDEHEART registry[15] did not support the use of dual antiplatelet agents, this analysis was performed on the overall MINOCA cohort, without discerning those with confirmed plaque disruption from those with other causes for MINOCA. A second antiplatelet agent may be reasonable based on extrapolation from AMI clinical trials that did not require confirmation of obstructive CAD and that showed an incremental benefit from the addition of a $P2Y_{12}$ receptor inhibitor to aspirin.[87,88]

It is not our practice to routinely stent patients with MINOCA and plaque rupture or erosion. This is supported by a small study of patients treated with dual antiplatelet therapy alone, which showed an acceptable 1-year revascularization rate of 5.7% in patients with MINOCA who were treated medically.[89]

Epicardial Coronary Vasospasm

Calcium channel blockers are the cornerstone therapy for patients with coronary spasm given their mechanism of action on calcium transduction, documented ability to suppress angina symptoms in vasospastic angina patients,[90] and evidence showing their absence is an independent determinant of cardiovascular events in vasospastic angina.[91] In patients with refractory vasospastic angina, the use of 2 calcium channel blockers (operating via different receptors) has been shown to alleviate symptoms.[92] Although short-acting sublingual and intracoronary nitrates are beneficial in acutely alleviating coronary spasm, the benefits of long-acting nitrates are less clear,[45] possibly because of issues with nitrate tolerance. Other agents shown to effectively alleviate coronary spasm include nicorandil (a potassium channel opener that also has nitrate properties) and cilostazol (a phosphodiesterase 3 inhibitor).[45]

Coronary Microvascular Dysfunction

The management of coronary microvascular dysfunction is limited, because revascularization therapies are not an option, and many conventional antianginal vasodilator drugs are less effective on the microvasculature than on large epicardial vessels.[49] Furthermore, the mechanisms responsible for the microvascular dysfunction differ between patients with this heterogeneous disorder, which could account for the discordant results between clinical trials[49] that have included patients with ischemia with nonobstructive CAD rather than MINOCA. Among the conventional antianginal therapies, calcium channel blockers and β-blockers have been shown to be beneficial in alleviating symptoms, whereas nitrates are less effective.[49] In addition, several small randomized, controlled clinical trials have demonstrated the efficacy of a variety of unconventional antianginal therapies, which exert their benefit by improving endothelial function (eg, L-arginine,[93] statin therapy,[94] enalapril[95]) or promoting microvascular vasodilation (eg, dipyridamole,[96] ranolazine[97]) or via a visceral analgesic effect (imipra-

mine,[98] aminophylline[99]). These studies largely excluded patients with AMI, and clinical trials specifically focusing on the management of patients with MINOCA who have coronary microvascular dysfunction are required.

Coronary Embolism/Thrombosis

It is open to speculation whether lifelong anticoagulant or antiplatelet therapies are justified in MINOCA patients who have evidence of coronary embolism/thrombosis. This requires more detailed investigation. Coronary thrombosis is usually treated with antithrombotic therapies and sometimes antiplatelet therapies. Certain conditions require additional therapies; for example, TTP is treated with plasma infusions supported by apheresis to allow plasma exchange, along with adjunctive therapies including steroids and rituximab. This has resulted in a markedly increased survival[65] for patients with TTP. Patients with HIT should avoid subsequent exposure to heparin molecules. Because of the complexity of the conditions described, a formal consultation with a hematologist should be considered.

Spontaneous Coronary Artery Dissection

There is currently no randomized prospective study addressing the appropriate treatment of SCAD in the acute or postacute phase. In the acute phase, it is common practice to avoid the use of percutaneous coronary intervention or stenting unless the patient is unstable or presenting with ST-segment–elevation myocardial infarction with a completely occlusive coronary artery.[100] This recommendation is based on observations that in most cases, coronary segments with SCAD heal spontaneously, and revascularization is associated with high complications, such as propagation of the dissection and intramural hematoma. Medical management of SCAD is also not well established. These patients are commonly treated with β-blockers and aspirin. Observational data indicated lower risk among patients with SCAD prescribed β-blockers.[74] The use of anticoagulant and dual antiplatelet therapy in the immediate management of medically treated SCAD remains controversial. These agents theoretically pose an increased risk of bleeding and propagation of the hematoma/dissection plane. On the other hand, some researchers argue that the intimal tear encountered in some SCAD patients can be prothrombotic and that the use of a moderately potent $P2Y_{12}$ inhibitor such as clopidogrel may be reasonable.[101] The use of other cardioprotective medications should be individualized based on the patient's specific risk factors and left ventricular abnormalities (eg, wall motion, CMRI findings, decreased ejection fraction). Although not proven in long-term studies, some experts recommend that patients avoid strenuous exercise and future pregnancies.[102]

Supply-Demand Mismatch

It is intuitive that the management of a MINOCA event resulting from a supply-demand mismatch would largely focus on the treatment or reversal of the inciting cause. Additional cardioprotective therapies should be individualized to each patient's clinical scenario.

PROGNOSIS

The prognosis of patients presenting with MINOCA depends on the underlying cause and is currently under active investigation. Most studies have shown that MINOCA patients have better outcomes than their AMI-CAD counterparts.[5,6,10] However, this finding is not consistent among all reports. In the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients),[16] patients with MINOCA had similar 1-month and 1-year mortality rates and comparable quality-of-life measures as patients with AMI-CAD. The Korean Infarct Registry showed that MINOCA patients had a similar risk of major adverse events as AMI-CAD patients with single- or double-vessel angiographic disease.[103] Furthermore, there is a substantial risk of recurrent events during follow-up of MINOCA patients that is higher than what is observed in the general population without cardiovascular disease.[14] Approximately 25% of patients with MINOCA will experience angina in the subsequent 12 months, which is similar to the frequency reported in patients with AMI-CAD.[104]

In the ACTION-GWTG registry (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With The Guidelines), in-hospital mortality in 19 000 MINOCA patients was 1.1%, with no sex differences observed.[5] A meta-analysis of MINOCA studies demonstrated similar results, with a pooled in-hospital mortality rate of 0.9% but a pooled 12-month mortality rate of 4.7%.[6] In the ANZACS-QI registry (All New Zealand Acute Coronary Syndrome–Quality Improvement), death or AMI occurred in 4.6% of MINOCA patients over 2 years compared with 2.2% of age- and sex-matched subjects without cardiovascular disease or diabetes mellitus.[14] In the SWEDEHEART study (mean follow up, 4.1 years), mortality was 13.4%; 7.1% of patients experienced another myocardial infarction, 4.3% had ischemic stroke, 6.4% were hospitalized for heart failure, and hospitalization for bleeding occurred in 3.6%.[15] Interestingly, less than half of all deaths were classified as cardiovascular. One-year mortality in young patients with MINOCA is reportedly lower (1.7%).[16]

Predictors of in-hospital mortality in MINOCA are similar to those in AMI-CAD (eg, age, higher troponin level, renal dysfunction, heart rate, blood pressure, peripheral arterial disease).[5,105] Interestingly, the presence of ST-segment elevation on the ECG and presentation with heart failure or shock were more strongly predictive of in-hospital death among patients with MINOCA than among those with AMI-CAD.[5] There are limited data on outcomes of MINOCA patients based on the

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presence or absence of angiographic atherosclerosis or specific underlying causes.

SPECIAL CONSIDERATIONS AND FUTURE DIRECTIONS

It is likely that the newer high-sensitivity troponin assays will increase the number of patients appropriately and inappropriately diagnosed with MINOCA. Therefore, we wish to emphasize the importance of following the proposed algorithm so that only appropriate patients are identified as having MINOCA. Clinicians should consider a working diagnosis of MINOCA only in those patients who have a clinical presentation suggesting a true AMI as defined by the "Fourth Universal Definition of Myocardial Infarction" (2018)[13] (ie, a clinical presentation consistent with myocardial ischemia and a rising or falling pattern of cardiac enzymes).

Currently, because of the lack of a specific diagnostic code, it is difficult to identify and track patients with MINOCA in administrative databases and many large registries. Although there is an *International Classification of Diseases–Tenth Revision* code that refers to "other MI" (I21.9), this code is not specific for MINOCA. The evaluation of patients with MINOCA frequently requires additional studies (eg, CMRI, IVUS, OCT, physiological testing, hematologic testing), and therefore resources, to define its underlying cause. As such, we advocate for a MINOCA-specific *International Classification of Diseases–Tenth Revision* code that is separate from traditional AMI diagnosis codes. This would provide the ability to detect patients with MINOCA, for clinical research and billing purposes, and would enable hospitals to pursue higher levels of reimbursement, if necessary, to offset the cost of additional diagnostic studies in these patients. To balance the increased use of resources needed to establish the underlying cause of MINOCA, we hope that by identifying the cause, providers will more efficiently target disease-specific therapies, ultimately leading to an improvement in clinical outcomes and lower downstream costs.

As mentioned previously, the angiographic assessment of a lesion and a physician's determination of lesion severity are often subjective, with substantial variability in reporting of severe lesions. For this reason, it is unclear at the current time whether all moderate lesions (ie, 30%–50%) should undergo FFR. Although we propose consideration for FFR assessment in selective, appropriate cases, future studies are needed to determine the number of patients with presumed MINOCA who have functionally significant stenosis and whether there is a role for the routine use of FFR in patients with a working diagnosis of MINOCA.

Additional research is needed to determine the optimal therapy for individuals with MINOCA based on the specific cause of the syndrome in those for whom a cause is identified and in those with MINOCA of unclear origin.[10] Large, multicenter randomized clinical trials are needed to determine the efficacy of traditional agents used in the secondary prevention of AMI at improving short- and long-term clinical outcomes. Candidate therapies to be investigated would include typical secondary prevention medications after AMI, such as β-blockers, ACE inhibitors/ARBs, statins, and antiplatelet agents, as well as calcium channel blockers, which directly address coronary artery spasm but are not part of the typical secondary prevention regimen after AMI.

Although our proposed algorithm attempts to improve the appropriate identification of patients with MINOCA and the underlying cause, the evaluations outlined here are neither sensitive nor specific, and until more data become available, clinical judgment and individualized care are essential.

CONCLUSIONS

MINOCA is a distinct clinical diagnosis with many different pathophysiological causes. It is essential that healthcare professionals become familiar with this syndrome so that patients are appropriately identified and treated. A working diagnosis of MINOCA should only be considered in those patients with a definite AMI (defined according to the "Fourth Universal Definition of Myocardial Infarction"),[13] nonobstructive disease on coronary angiography, and no other clinical entities that would lead to myocardial injury without ischemia. The optimal evaluation for patients with a diagnosis of MINOCA, after the exclusion of other causes for troponin elevation, should be aimed at determining the specific cause for each patient so that targeted therapies can be used. It is our hope that this newly revised definition of MINOCA and the proposed algorithm for its assessment will lead to a better understanding of the prevalence and treatment of the various conditions that result in MINOCA and to improved clinical outcomes.

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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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