Journal of the American Heart Association

MINI-REVIEW

Role of Multimodality Imaging in the Assessment of Myocardial Infarction With Nonobstructive Coronary Arteries: Beyond Conventional Coronary Angiography

Brent Gudenkauf, MD; Allison G. Hays, MD; Jacqueline Tamis-Holland, MD; Jeffrey Trost, MD; Daniel I. Ambinder, MD; Katherine C. Wu, MD; Armin Arbab-Zadeh, MD, PhD, MPH; Roger S. Blumenthal, MD; Garima Sharma, MD

ABSTRACT: Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous clinical entity, encompassing multiple different causes, and a cause of substantial morbidity and mortality. Current guidelines suggest a multimodality imaging approach in establishing the underlying cause for MINOCA, which is considered a working diagnosis. Recent studies have suggested that an initial workup consisting of cardiac magnetic resonance and invasive coronary imaging can yield the diagnosis in most patients. Cardiac magnetic resonance is particularly helpful in excluding nonischemic causes that can mimic MINOCA including myocarditis and Takotsubo cardiomyopathy, as well as for long-term prognostication. Additionally, intracoronary imaging with intravascular ultrasound or optical coherence tomography may be warranted to evaluate plaque composition, or evaluate for plaque disruption or spontaneous coronary dissection. The role of noninvasive imaging modalities such as coronary computed tomography angiography is currently being investigated in the diagnostic approach and follow-up of MINOCA and may be appropriate in lieu of invasive coronary angiography in select patients. In recent years, many strides have been made in the workup of MINOCA; however, significant knowledge gaps remain in the field, particularly in terms of treatment strategies. In this review, we summarize recent society guideline recommendations and consensus statements on the initial evaluation of MINOCA, review contemporary multimodality imaging approaches, and discuss treatment strategies including an ongoing clinical trial.

Key Words: angiography ■ computerized tomography ■ magnetic resonance imaging ■ myocardial infarction ■ optical coherence tomography

Cardiovascular disease remains the leading cause of death in the United States, with 659 041 deaths in 2019.[1] Although there has been a decline in coronary artery disease (CAD)-related mortality with contemporary treatment approaches, most current therapies are directed at the predominant cause of myocardial infarction—coronary arterial plaque disruption and thrombosis.[2] However, early coronary angiography studies documented that a notable number of patients with acute myocardial infarction (MI) demonstrated no significant coronary artery obstruction, termed myocardial infarction with nonobstructive coronary arteries (MINOCA).[2] Before the more widespread recognition of MINOCA by major cardiovascular societies, some regarded MINOCA patients as having "false-positive MI," thus minimizing the need for further diagnostic workup or targeted medical therapy.[3–5] To improve the recognition and evaluation of patients with MINOCA, the American Heart Association and the European Society of Cardiology have outlined specific diagnostic criteria (Figure 1).[5–8] To diagnose MINOCA one must have positive serum myocardial biomarkers

Correspondence to: Garima Sharma, MD, FACC, Division of Cardiology, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Carnegie 565C, 600 N Wolfe Street, Baltimore, MD 21287. E-mail gsharma8@jhmi.edu

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

MI-CAD	myocardial infarction associated with obstructive coronary artery disease
MINOCA	myocardial infarction with nonobstructive coronary arteries
RAPID-CTCA	Rapid Assessment of Potential Ischaemic Heart Disease with CTCA trial
SCAD	spontaneous coronary dissection
TC	Takotsubo cardiomyopathy
VERDICT	Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients with Acute Coronary Syndromes Trial

(preferentially cardiac troponin) with at least 1 level rising above the 99th percentile of the upper limit of normal.[5,6] Additionally, they have clinical evidence of MI, manifested by ischemic symptoms, new ST-segment changes, a new left bundle-branch block, new pathological Q waves on electrocardiogram, imaging evidence of loss of viable myocardium or new regional wall motion abnormalities, or an intracoronary thrombus. To diagnose MINOCA, there must be no epicardial coronary lesions of >50% stenosis on coronary angiography, which constitute significant obstructive disease. Finally, there must be no overt alternative diagnosis to explain the clinical presentation.[5–8]

Subsequent investigations have estimated the prevalence of MINOCA at around 6% of all patients with MI, with a wide estimated range of 1% to 14%, which likely reflects variability in the populations studied and the manner in which MINOCA was defined.[2,9,10] Autopsy analysis suggests a much larger prevalence in young people who die of ischemic heart disease, with pathologic evidence of MI in 43% of cases, 17% of whom had nonobstructive CAD overall. MINOCA was especially prevalent in women in this study (23% with nonobstructed coronary arteries, as compared with 16% of men).[11] MINOCA patients typically have fewer traditional risk factors for CAD in comparison to patients with MI associated with obstructive CAD (MI-CAD); they are younger and more likely to be female.[9,10,12]

As MINOCA is a heterogeneous syndrome, the long-term prognosis is likely dependent upon the underlying cause. Taken together, however, these patients are estimated to have a 0.9% in-hospital all-cause mortality, and 4.7% mortality at 12-months.[9] Pooled data from observational studies initially showed that MINOCA is associated with decreased in-hospital mortality in comparison to MI-CAD, but more recent data have challenged these findings, demonstrating a similar prognosis for patients with MINOCA and MI-CAD.[13,14] One study revealed that MINOCA patients have similar rates of 12-month mortality when compared with patients with obstructive disease in 1 or 2 coronary arteries, but rates of major adverse cardiac events differ substantially (3.1% in MINOCA versus 3.2% 12-month mortality, and 7.8% in MINOCA versus 12.2% 12-month major adverse cardiac events in patients with 1 or 2 vessel CAD).[15] It is important to note, however, that both categories of patients fare better than those with triple-vessel or left main disease (with 6.5% 12-month mortality and 23.3% major adverse cardiac events).[15] MINOCA portends a worse prognosis than stable angina, which has a 0.2% annual all-cause mortality rate, and an adverse event rate double that of a similar cohort without cardiovascular disease.[9,16]

Further, long after the diagnosis of MINCOA is established, 25% of these patients will continue to experience angina.[17] In one study, MINOCA patients, as compared with patients with MI-CAD, were found to experience worse quality of life because of angina and lower satisfaction with antianginal treatment, were less often treated with beta blockers, and were less often referred to cardiac rehabilitation.[17] For these reasons, it is important to identify the underlying cause of MINOCA so that patients can receive therapies that target the specific cause. This review aims to summarize recent guidelines and advances in multimodality imaging approaches in the diagnostic and prognostic approach to MINOCA.

CLINICAL PRESENTATION AND PATHOGENESIS OF MINOCA

The clinical presentation of MINOCA is similar to MI-CAD, although traditional risk factors for MI vary in this population. In comparison to patients with MI-CAD, patients with MINOCA are more likely to be female (95% CI, 35%–51% versus 19%–30%), younger (95% CI, 51.6–66.1 years versus 52.2–70.4 years) and have less hyperlipidemia (95% CI, 6%–35% versus 30%–59%).[9,10,12] Further, patients with MINOCA are less likely to smoke cigarettes (21% versus 33%) and have impaired glucose tolerance (39% versus 55%) in comparison to patients with MI-CAD[12]; notably, one review showed that 14% of patients with MINOCA had underlying thrombophilia.[9]

The pathophysiology of MINOCA is variable and is typically divided into those resulting from plaque disruption (plaque rupture, erosion, or calcific nodule) and those resulting from other epicardial and microvascular causes (in situ thrombosis, spontaneous coronary dissection [SCAD], epicardial or microvascular spasm,

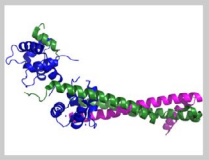
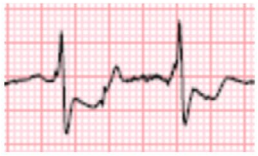
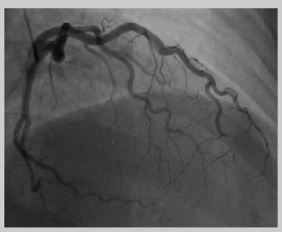
Diagnostic Criteria of Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA)		
Myocardial infarction	Rise and fall of myocardial biomarkers in serum (preferentially cardiac troponin), with one level >99th percentile of upper limit of normal for assay.	
	Ischemic symptoms OR signs (new ST-T segment changes, new LBBB, new pathological Q waves, imaging evidence of loss of viable myocardium or new RWMA, or intracoronary thrombus).	
Nonobstructive coronary arteries on angiography	No stenosis >50% in any infarct-related epicardial artery, including patients with normal arteries (0 to 30% stenosis) or mild atheromatous disease (30 to <50% stenosis). All vessels must have FFR >0.80.	
No other cause of the acute presentation	Lack of an overt alternative diagnosis (eg, sepsis, pulmonary embolism, cardiac contusion).	

Figure 1. Diagnostic criteria of MINOCA.[5,8]
FFR indicates Fractional flow reserve; LBBB, left bundle-branch block; and RWMA, regional wall motion abnormality.

and coronary embolism).[5,18] The European Society of Cardiology guidelines and the American Heart Association consensus document emphasize the importance of considering MINOCA as a "working" diagnosis, with further study being necessary both at the bedside and beyond.[5,8]

DIAGNOSTIC PATHWAYS

The diagnostic imaging pathway best pursued should be based on the clinician's differential diagnosis after reviewing pertinent clinical information, in particular the coronary angiogram. Importantly, the American Heart Association Scientific Statement on MINOCA suggests a careful rereview of the coronary angiogram to ensure that subtle coronary obstructive disease is not overlooked (eg, complete occlusion of a small subsegmental artery, or missed significant stenoses of small branches).[5] Once obstructive stenosis is excluded, and the working diagnosis of MINOCA is established, a multimodality imaging approach should be pursued to further refine the diagnostic subtype and identify the underlying pathology.

If coronary angiography is normal or demonstrates nonobstructive plaque, then intracoronary evaluation with intravascular ultrasound (IVUS) or optical coherence tomography (OCT) might be considered.[5,8] If the patient's history suggests vasospasm or microvascular spasm, then early coronary functional assessment with acetylcholine may be indicated, although studies verifying safety in the setting of acute MI are limited.[6] In a recent study, coronary angiography was performed one minute after intracoronary injection of acetylcholine or ergonovine and analyzed using computer software.[19] After this initial analysis, intracoronary nitroglycerin was administered, with further computer-assisted analysis. This challenge diagnosed 46.2% of patients with vasospasm.[19] Epicardial spasm was diagnosed when a diameter reduction of 90% or greater was detected in response to acetylcholine or ergonovine challenge, and microvascular spasm was diagnosed when ischemic ST-segment changes and angina developed in the absence of epicardial coronary constriction in response to challenge. Other recent studies found 13% to 24% of patients presenting with MINOCA had coronary vasospasm.[13,20] Although there were initial safety concerns with early provocative testing with ergonovine, only 5.4% of patients experienced arrhythmic complications during testing, which is similar to the occurrence rate during spontaneous angina.[19]

If embolism to the coronary arteries is strongly suspected clinically, then thrombophilia workup, appropriate microbiologic workup, and transesophageal echocardiogram to evaluate for intracardiac clot or valvular vegetation may be considered if results would change management.[5–8] Several thrombophilias have been identified in patients with MINOCA, including factor V Leiden, the prothrombin G20210A mutation, protein S deficiency, and the antiphospholipid antibody syndrome.[9] As up to 14% of patients with MINOCA may be affected and thus at risk for repeated episodes of thromboembolism, it would be reasonable to screen for these conditions.[9]

Cardiac magnetic resonance imaging (CMR) is useful to evaluate patients with suspected MINOCA and its use is strongly supported by the recent European Society of Cardiology guidelines for management of acute coronary syndromes. The presence of late gadolinium enhancement will help to confirm a diagnosis of MINOCA.[21] Additionally, magnetic resonance imaging may uncover MINOCA mimics such as myocarditis, Takotsubo cardiomyopathy (TC), or other nonischemic cardiomyopathies. If it shows myocardial necrosis, then the working diagnosis would be changed to an acute MI and angiography would be indicated. However, because MINOCA is diagnosed only in patients with a suspected acute MI who have nonobstructive disease, magnetic resonance imaging should not be the first test employed to evaluate these patients.

Our suggested diagnostic algorithm is shown in Figure 2.

MULTIMODALITY IMAGING IN THE ASSESSMENT OF MINOCA

Here we discuss the various imaging modalities that may be used in the diagnostic workup and prognostication of MINOCA.

ROLE OF INVASIVE INTRACORONARY IMAGING IN MINOCA

Intravascular ultrasound (IVUS) has been long used in clinical practice to characterize and quantify coronary plaque with adequate depth, and to assist with percutaneous intervention. Optical coherence tomography (OCT) is a newer intravascular imaging method that produces high resolution images of coronary plaque. The principle of OCT is similar to IVUS, but OCT uses infrared light rather than ultrasound. The advantage of OCT is that the technique can characterize plaque composition, but it has reduced depth and coverage compared with IVUS. Although OCT provides superior image resolution compared with IVUS, it is not yet widely available and is limited in patients with chronic kidney disease because of the need for additional contrast infusion during imaging.[22]

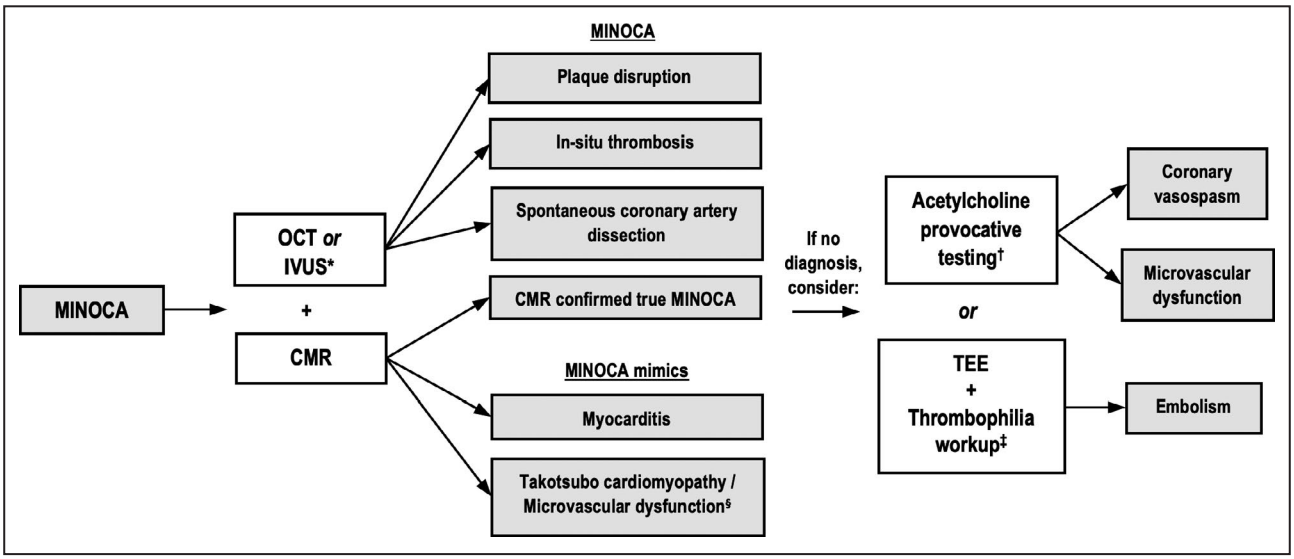


Figure 2. Suggested diagnostic algorithm for the workup of MINOCA.
Imaging modalities are in white, and corresponding diagnoses in gray. *Triple-vessel intracoronary imaging is recommended to increase diagnostic yield. †Functional assessment can be considered at any time if the history is suggestive of vasospasm or the patient has other vasospastic disease such as Raynaud's phenomenon or cerebral vasospasm.[11] ‡If embolism to the coronary arteries is strongly suspected clinically, then thrombophilia workup and transesophageal echocardiogram to evaluate for intracardiac clot or valvular vegetation may be considered if results would change management. §Assessment of microvascular dysfunction on CMR may require the use of rest and stress perfusion analysis. CMR indicates cardiac magnetic resonance; IVUS, intravascular ultrasound; MINOCA, myocardial infarction with nonobstructive coronary arteries; OCT, optical coherence tomography; and TEE, transesophageal echocardiogram.

These invasive imaging modalities have an important role in the diagnostic workup of MINOCA; they are most useful for characterizing plaque ruptures, as well as detecting coronary artery dissection. One study of women diagnosed with MINOCA found that IVUS was able to yield a diagnosis of plaque rupture in 38% of patients.[21] Another study found a 37% rate of plaque rupture in MINOCA patients.[23] OCT might be expected to have a higher diagnostic yield owing to its superior spatial resolution. Two recent studies have sought to clarify the utility of OCT in MINOCA patients. OCT was able to yield a diagnosis in 80% of patients with MINOCA and wall motion abnormalities corresponding to ECG changes.[20] Most patients had plaque rupture (shown in Figure 3,[24]), followed by (in order of prevalence) plaque erosion (shown in Figure 4,[24]), in situ thrombosis, SCAD (shown in Figure 5,[24]), and eruptive calcific nodule.

Importantly, clarification of diagnosis by OCT changed clinical management in almost 30% of cases, with antiplatelet and antithrombotic agents initiated faster and for a prolonged duration in patients with plaque erosion, and with aspirin and beta blocker initiated early in patients diagnosed with SCAD.[20] A more recent study showed that 3-vessel OCT yielded a diagnosis in 46% of women with MINOCA, with the most-to-least common lesions being intraplaque cavity, layered plaque, plaque rupture, in situ thrombus, intimal bumping suggesting vasospasm, and SCAD.[25] The difference in diagnostic yield between the 2 studies may be explained by the former study (Gerbaud et al) performing a detailed analysis before proceeding with OCT including CMR and provocative intracoronary testing, and by the latter study pursuing a 3-vessel OCT approach rather than one targeted toward the likely culprit vessel only.

The timing of OCT is important in the evaluation of MINOCA. A recent study found that the diagnostic yield of OCT decreased as time-to-OCT increased, with normal OCT examination in only 7% of patients when performed in conjunction with angiography, but normal OCT in 27% of patients when performed as a second diagnostic procedure.[26] Furthermore, the study reported no complications with the addition of OCT, although significantly more iodinated contrast was used (51 mL additional contrast). The authors suggest that when feasible, OCT should be performed in all epicardial coronaries, as culprit lesions in women with MINOCA were found to rarely be located at the most stenotic lesions on angiography and 3-vessel OCT increases diagnostic yield.[26] Further, recent work in this field has demonstrated that plaque disruption may be detected on intracoronary imaging even in patients with normal angiograms.[25]

Taken together, these initial studies are compelling and show a high diagnostic yield using OCT for the workup of MINOCA, particularly when performed at the same time as angiography. Although the diagnostic utility of OCT is promising, future studies are needed to evaluate to what extent OCT affects treatment decisions compared with standard coronary angiography and whether this results in improved long-term

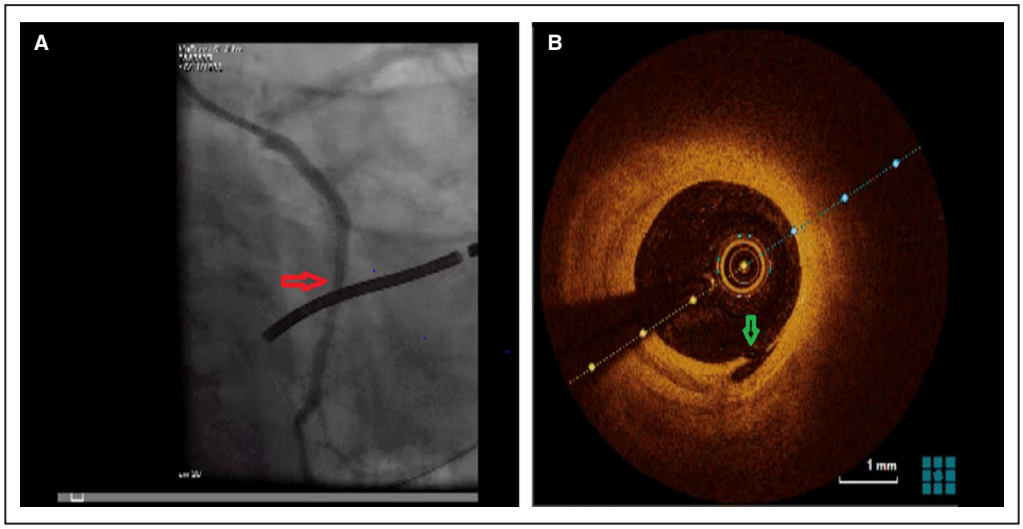


Figure 3. Case of a 55-year-old woman with hypertension presenting with chest tightness and T wave inversion in lateral leads and abnormal cardiac biomarkers.
A, Coronary angiogram demonstrated nonobstructive lesion in mid LCX (red arrow). **B**, OCT images demonstrated a plaque rupture (green arrow). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Current Cardiology Reports*, The Imaging Toolbox to Assess Patients with Suspected Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease (MINOCA), Soheila Talebi, Pedro Moreno, Abel Casso Dominguez, and Jacqueline E. Tamis-Holland. Copyright ©2020.[24] LCX indicates left circumflex artery; and OCT, optical coherence tomography.

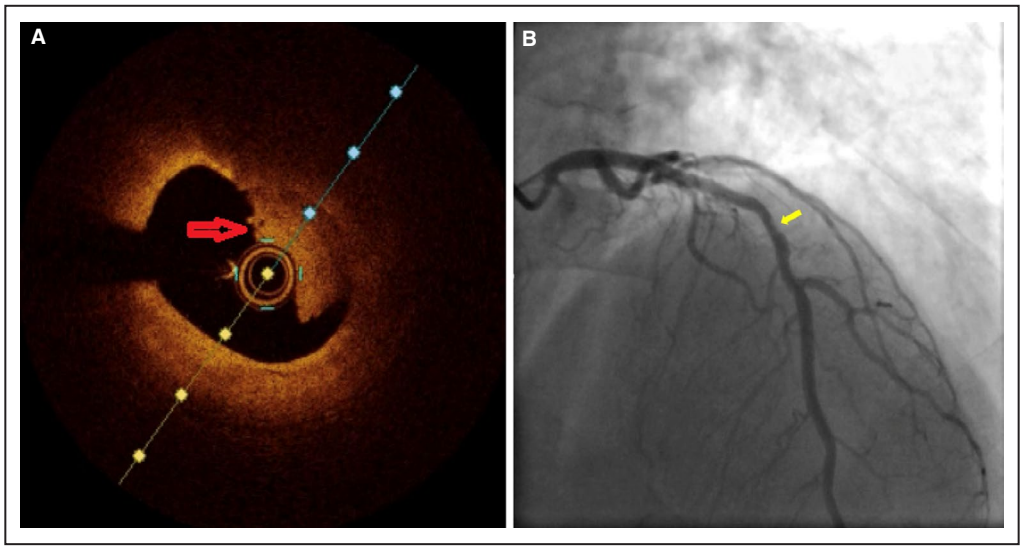


Figure 4. Case of a 66-year-old man with no past medical history who presented with chest pain and dyspnea, ST elevation in lateral and inferior leads, and elevated cardiac biomarkers.
A, OCT images demonstrating a thrombus overlying an intact fibrous cap in mid-LAD, consistent with plaque erosion (red arrow). **B**, Coronary angiogram with nonobstructive lesion in mid-LAD (yellow arrow). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Current Cardiology Reports*, The Imaging Toolbox to Assess Patients with Suspected Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease (MINOCA), Soheila Talebi, Pedro Moreno, Abel Casso Dominguez, and Jacqueline E. Tamis-Holland. Copyright ©2020.[24] LAD indicates left anterior descending artery; and OCT, optical coherence tomography.

outcomes. It is important to note that intracoronary imaging adds risk and cost to the angiographic procedure, particularly in a patient with suspected SCAD (for example, a young woman with family history of fibromuscular dysplasia, who has no risk factors for atherosclerosis, and with angiogram demonstrating gradual luminal narrowing that may represent type 3 SCAD). For this reason, the benefits of intracoronary

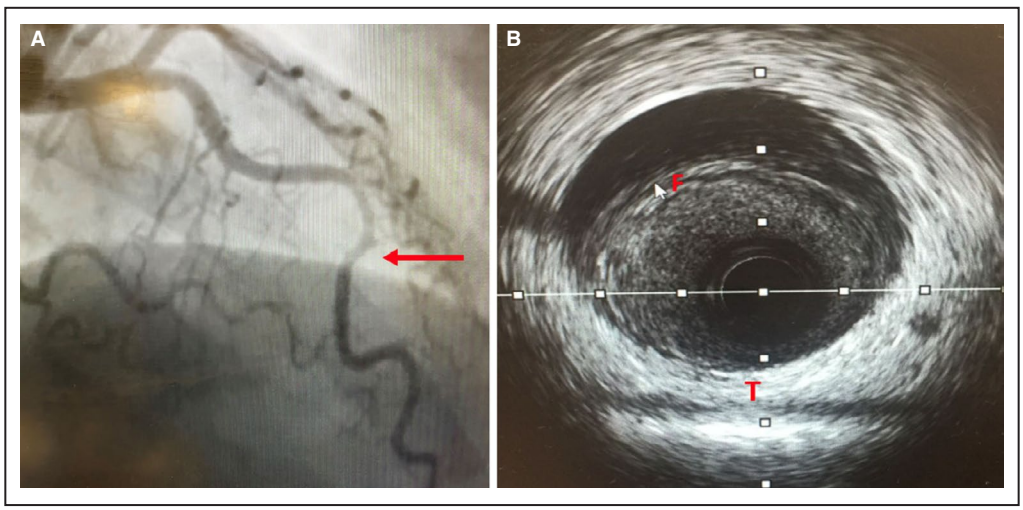


Figure 5. Case of a 42-year-old man without past medical history presenting with chest pain, mild T wave abnormalities in the anterior wall, and elevated cardiac biomarkers.
A, Coronary angiogram demonstrated nonobstructive lesion in the mid-LAD (red arrow). **B**, IVUS imaging demonstrated classical findings of SCAD with true lumen (T) and false lumen (white arrow) (F). Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Current Cardiology Reports*, The Imaging Toolbox to Assess Patients with Suspected Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease (MINOCA), Soheila Talebi, Pedro Moreno, Abel Casso Dominguez, and Jacqueline E. Tamis-Holland. Copyright ©2020.[24] IVUS indicates intravascular ultrasound; LAD, left anterior descending artery; and SCAD, spontaneous coronary dissection.

imaging in arriving at a diagnosis to inform treatment should be carefully weighed against the theoretical risk of dissection propagation from instrumentation, although it is important to note that no such complications occurred in these recent studies.[20–23,25,26] Additionally, the injection of flush media with OCT may induce ischemia by clearing the vessels of blood, and thus OCT should be used with caution in patients with severe hemodynamic instability.

ROLE OF CARDIOVASCULAR MAGNETIC RESONANCE IMAGING IN MINOCA

CMR imaging has emerged as the gold standard for noninvasive assessment of cardiac function and morphology because of its safety, interobserver consistency, quantitative accuracy, and ability to characterize the myocardium. CMR can detect infarct-related edema by T2-weighted imaging, as well as fibrosis based on late gadolinium enhancement, as in Figure 6.[27] Gadolinium-enhanced CMR has been shown to be highly sensitive for the detection of infarction, able to quantify infarcts as small as 0.16 g.[28,29] Early gadolinium enhancement and T1 imaging can detect hyperemia seen in acute myocarditis as well, which can be distinguished from chronic myocarditis by T2-weighted imaging.[30,31] Newer T1 and T2 parametric mapping sequences have the potential to enhance the ability of CMR to identify a cause of MINOCA.[32] Accordingly, CMR is a key diagnostic tool in the evaluation of patients presenting with MINOCA, though current published studies are limited by relatively small numbers and heterogeneity in study design, patient selection and characteristics, CMR protocols, and timing from troponin elevation to CMR study. CMR can provide an etiologic diagnosis in as many as 77% to 87% of cases, depending on the cohort.[33–35] However, in many cases no specific diagnosis may be determined (eg, no edema or fibrosis is visualized) and the patient has CMR-confirmed true MINOCA.

Shorter time interval between clinical presentation and CMR imaging improves diagnostic yield. Studies in which CMR was performed at ≈3 days following presentation yielded diagnoses in 77% to 86% of patients,[32,36] compared with 47% when CMR was performed at a median of 12 days after presentation.[34] When CMR is performed later in the course of a patient's illness, almost two thirds of patients had normal findings and myocarditis was diagnosed in only 7% of patients.[34] A recent meta-analysis of 42 CMR studies

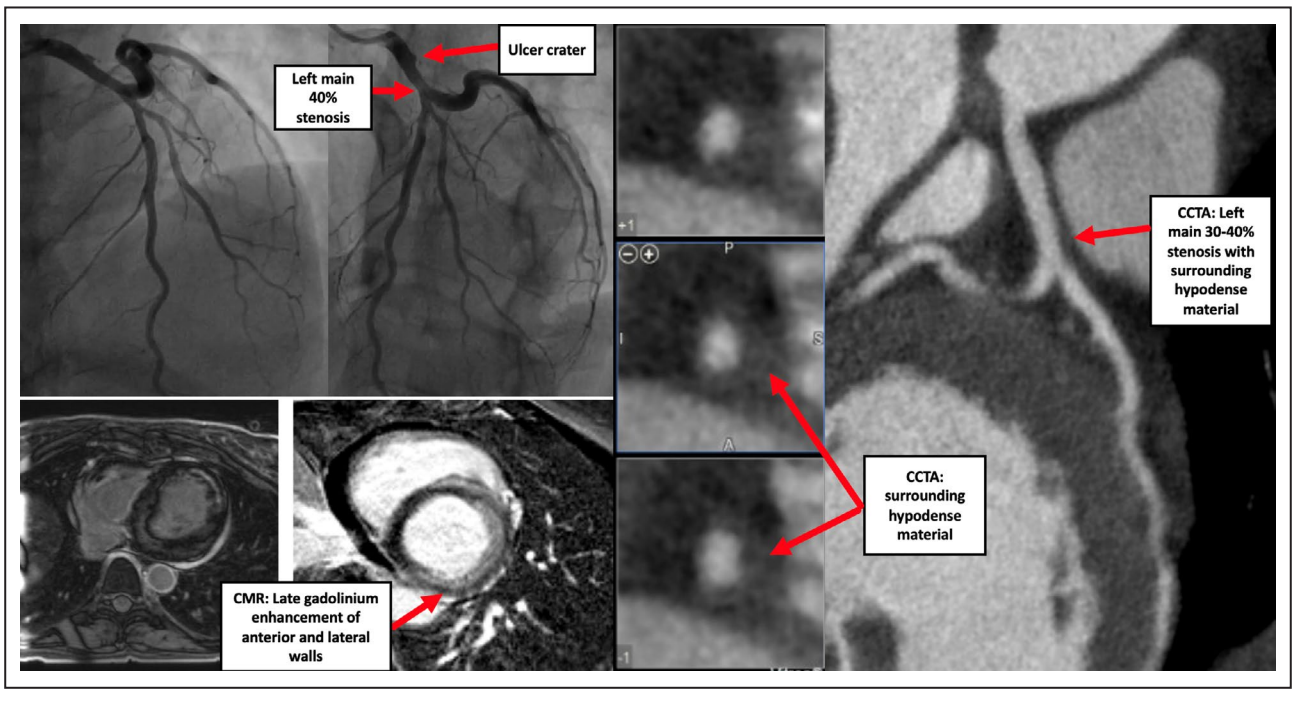


Figure 6. Case of a 42-year-old woman who presented with syncope, ventricular tachycardia, and elevated troponin. Coronary angiography indicated an ulcer crater in the left main coronary artery with 40% stenosis which extended into the origin of the LAD and the LCX. CMR showed delayed transmural gadolinium enhancement in the anterior and lateral walls as well as the lateral aspect of the inferior wall, suggestive of a vascular insult. CCTA was performed to further evaluate the lesions seen on angiography, finding 30% to 40% stenosis of distal left main, with surrounding hypodense material causing vessel enlargement, suggestive of SCAD with intramural hematoma. Similar findings were seen in the very proximal portions of the LAD and LCX. No atherosclerosis was observed. CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; LAD, left anterior descending artery; LCx, left circumflex artery; and SCAD, spontaneous coronary dissection.

performed in the subacute phase encompassing 5821 patients reported a pooled prevalence of myocarditis at 26%, TC at 11%, and another cardiomyopathy at 7%.[37]

There are limited studies evaluating the prognostic value of CMR findings in patients with MINOCA and disparate findings likely reflect study design and selection bias. A recent prospective multicenter registry found that late gadolinium enhancement involving 3 or more segments (versus a single segment with late gadolinium enhancement) was associated with triple the risk of major adverse cardiovascular events with CMR performed at a median of 12 days following admission.[38] In contrast, a retrospective study in which CMR was performed at a median of 37 days after presentation reported that cardiomyopathy was associated with worse prognosis (15% mortality at 3.5 years) compared with MI (4% mortality rate at 3.5 years).[39]

A recent prospective, multicenter study focused on women presenting with MINOCA, in whom CMR was performed within a week of acute presentation (median of 6 days), found an ischemic pattern of late gadolinium enhancement in 33% of women (with 95% having concomitant myocardial edema), and regional edema was observed in almost 21% (as shown by increased T2-weighted signal in the territory of a single coronary artery).[25] Myocarditis was detected in 14.7%, TC in 3.4%, and nonischemic cardiomyopathy in 2.6% as the alternative causes of elevated troponins; 25.9% of women had normal CMRs.[25] The lower incidence of myocarditis in this cohort likely reflects the exclusion of clinical myocarditis, older average age of the cohort (median of 60 years), and decreased prevalence of myocarditis in women. In this study, multimodal imaging with OCT was further added to CMR and improved identification of potential mechanisms of myocardial injury in 85% of women, 75.5% of which were ischemic (ie, true MINOCA), and 24.5% of which were nonischemic. Importantly, the diagnostic yield with the combination of OCT and CMR was significantly higher at 84.5% than the yield from either alone (44% for OCT and 74% for CMR), leaving only 15.5% of patients with no imaging findings to suggest a cause for the clinical presentation.[25]

Reynolds et al previously found that CMR and IVUS are complementary approaches to achieving a diagnosis, but the diagnostic yield was lower with these techniques.[21] In another study evaluating patients with MINOCA, CMR diagnosed ischemia in 77.5% of patients, with 12.5% of patients demonstrating multiple hyperenhanced lesions supporting coronary embolization.[20] Impressively, the combination of OCT and CMR in this study yielded a diagnosis for 100% of patients with a working diagnosis of MINOCA. These recent studies suggest that precise diagnosis through combined use of OCT and CMR is feasible and both modalities provide independent and complementary diagnostic value.

TAKOTSUBO CARDIOMYOPATHY AS A CLINICAL ENTITY IN THE DIFFERENTIAL OF MINOCA

Although less prevalent than plaque rupture or myocarditis, TC is a frequent underlying cause of acute myocardial injury, responsible for about 1% to 2% of patients presenting with acute myocardial injury and often presents as a MINOCA "mimic."[40] TC carries a relatively favorable prognosis in comparison to MI secondary to atherosclerotic plaque rupture, as the myocardium is thought to be "stunned." It most frequently occurs in postmenopausal women and most often causes an apical ballooning pattern of left ventricular contraction, although this pattern can also be seen in SCAD and in plaque rupture of the left anterior descending artery.[40–42]

The underlying pathophysiology of TC is most likely due to microvascular dysfunction, with accumulating evidence indicating that acute increases in circulating catecholamines cause hyperreactivity of the microvascular endothelium and subsequent infarction of underlying myocardium.[43,44] Other pathophysiologic mechanisms proposed to account for this syndrome include direct myocardial toxicity, catecholamine receptor isotype switching, inhibition of endothelial nitric oxide synthesis, multivessel epicardial coronary artery spasm, MI with spontaneous recanalization, and others.[43] However, much about this condition is yet unknown. The predominance among postmenopausal women suggests that loss of ovarian hormones predisposes coronary microvasculature to dysfunction, but the specific mechanism is uncertain. Additionally, it is unclear why apical segments of the myocardium are most affected and in varying patterns.[41,42]

During angiography, an increased thrombolysis in myocardial infarction frame count may indicate increased resistance and decreased coronary flow reserve.[43] Patients with TC have globally reduced coronary flow, comparable to patients diagnosed with microvascular angina.[45] These perfusion abnormalities correlate strongly with degree of myocardial injury.[43]

TC can be diagnosed most readily through imaging with distinct wall motion patterns. Left ventriculography is a reasonable "first step" after the diagnosis of MINOCA is made on coronary angiography.[7] Echocardiography can also be used to quickly visualize ventricular dysfunction suggestive of TC, and speckle tracking has been used to track recovery of myocardial contraction after TC.[46,47] The patterns of TC, although readily recognized on CMR, are outside the purview of this manuscript and we briefly mention TC as a cause of myocardial injury (Figure 2).[48]

ROLE OF CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY IN MINOCA

Coronary computed tomography angiography (CCTA) can suggest ischemia or infarction by highlighting perfusion defects,[49,50] and it can sometimes detect ulceration, plaque fissures, as well as SCAD, but with less resolution than intracoronary imaging techniques.[51–53] A normal study is associated with excellent prognosis, and it allows redirection of remaining workup to nonischemic causes. A normal study also has management implications, as antiplatelet and statin use is likely not beneficial. However, it is important to note that CCTA may be less accurate in the acute setting because of general illness. Therefore, the prognostic implications of a negative CCTA may not apply to MINOCA patients. The recent VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography in Patients with Acute Coronary Syndromes) trial showed that although CCTA may effectively rule out obstructive disease in non-ST elevation acute coronary syndrome, with a negative predictive value of 91% and sensitivity of 97%, the RAPID-CTCA (Rapid Assessment of Potential Ischaemic Heart Disease with CTCA [CT Coronary Angiography]) trial found that early use of CCTA did not reduce death or subsequent MI in patients presenting with suspected acute coronary syndrome.[54,55]

CCTA may, however, assist in the follow-up of select patients with MINOCA, particularly patients with SCAD (the cause of about 1%–5% of MINOCA) if it was detected on initial imaging, as it can spare these patients repeated invasive angiography, which can theoretically precipitate further dissection. As SCAD occurs most often in younger adults, and particularly in women, there are concerns about exposing these patients to significant levels of ionizing radiation with serial imaging studies. These concerns may be mitigated with the use of CCTA protocols incorporating low-dose radiation (as little as 2 mSv).[56,57] It is important to note that CCTA should not be considered adequate to rule out dissection, as it is most sensitive for proximal dissections only. SCAD can be ruled out only with careful intracoronary imaging.

TREATMENT OF MINOCA

The prognosis and treatment of MINOCA vary greatly and depend on the extent of left ventricle dysfunction and may depend as well on the underlying cause. In patients found to have coronary vasospasm-related MI, calcium channel antagonism is associated with improved survival.[58] However, there are no randomized clinical trials evaluating treatments for patients with MINOCA due to other pathology.

Observational data from the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry provides some important insights; 9136 patients with MINOCA were observed after a mean 4.1-year follow-up period and 24% of patients had a major adverse cardiac event, with hazard ratios determined from the use of certain medication classes. Statin therapy was associated with the largest reduction in major adverse cardiac events at 23%, followed closely by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at 18%.[59] These findings corroborate results from OCT and CMR imaging studies that, like MI-CAD, atherosclerosis is the causative pathology in a large proportion of cases of MINOCA.

The MINOCA-BAT (β-Blocker and ACEI/ARB Treatment in MINOCA patients) trial is a multicenter study that has randomized patients with MINOCA to beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers in a 2-by-2 factorial design and will compare time to death of any cause, readmission for MI, and incidences of ischemic stroke and heart failure (clinicaltrials.gov, NCT 03686696).[60] The results of this trial will inform treatment strategies in the approach to different subtypes of MINOCA, where many knowledge gaps remain.

CONCLUSIONS

MINOCA is a heterogeneous clinical phenomenon and a cause of important morbidity and mortality. Current consensus documents suggest a multimodality imaging approach to further delineate the underlying pathophysiology of MINOCA once the working diagnosis is made. If the clinical evaluation suggests ischemia and an underlying cause is not obvious on invasive coronary angiography, one can consider a more specialized intracoronary imaging approach (IVUS, OCT, vasoreactive testing).

CMR should be strongly considered as a first-line imaging test for MINOCA to further refine the diagnosis. Further workup should be dictated by the results of invasive coronary imaging, CMR, and the clinical context. Observational data suggest that some MINOCA patients may benefit from statin therapy and angiotensin receptor inhibition or angiotensin receptor blockade, but an ongoing clinical trial should shed light on the optimal treatment algorithm for MINOCA subtypes.

ARTICLE INFORMATION

Received June 7, 2021; accepted November 30, 2021.

Affiliations

Division of Cardiology, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD (B.G., A.G.H., K.C.W., A.A., R.S.B., G.S.); Division of Cardiology, Mount Sinai-

Morning Side, New York City, NY (J.T.); and Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (J.T., D.I.A.).

Acknowledgments

The authors extend thanks to their colleagues in the Cardiovascular Interventional Laboratory and the Radiology divisions that made this work possible.

Sources of Funding

Dr Sharma is supported by the Blumenthal Scholarship in Preventive Cardiology.

Disclosures

None.

REFERENCES

1. Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999–2019 on CDC WONDER Online Database, released in 2020. Data are from the multiple cause of death files, 1999–2019, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available at: http://wonder.cdc.gov/ucd-icd10.html. Accessed April 13, 2021. 12:43:19 PM.
2. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med*. 1980;303:897–902. doi: 10.1056/NEJM198010163031601
3. Pasupathy S, Tavella R, Beltrame JF. Myocardial infarction with non-obstructive coronary arteries (MINOCA): the past, present, and future management. *Circulation*. 2017;135:1490–1493. doi: 10.1161/CIRCULATIONAHA.117.027666
4. McCabe JM, Armstrong EJ, Kulkarni A, Hoffmayer KS, Bhave PD, Garg S, Patel A, MacGregor JS, Hsue P, Stein JC, et al. Prevalence and factors associated with false-positive ST segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention-capable centers: a report from the Activate-SF registry. *Arch Intern Med*. 2012;172:864–871. doi: 10.1001/archinternmed.2012.945
5. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, et al. 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. *Circulation*. 2019;139:e891–e908. doi: 10.1161/CIR.0000000000000670
6. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
7. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575
8. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153. doi: 10.1093/eurheartj/ehw149
9. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870. doi: 10.1161/CIRCULATIONAHA.114.011201
10. Agewall S, Daniel M, Eurenius L, Ekenbäck C, Skeppholm M, Malmqvist K, Hofman-Bang C, Collste O, Frick M, Henareh L, et al. Risk factors for myocardial infarction with normal coronary arteries and myocarditis compared with myocardial infarction with coronary artery stenosis. *Angiology*. 2012;63:500–503. doi: 10.1177/0003319711429560
11. Smilowitz NR, Sampson BA, Abrecht CR, Siegfried JS, Hochman JS, Reynolds HR. Women have less severe and extensive coronary atherosclerosis in fatal cases of ischemic heart disease: an autopsy study. *Am Heart J*. 2011;161:681–688. doi: 10.1016/j.ahj.2010.12.022
12. Daniel M, Ekenbäck C, Agewall S, Brolin EB, Caidahl K, Cederlund K, Collste O, Eurenius L, Frick M, Younis-Hassan S, et al. Risk factors and markers for acute myocardial infarction with angiographically normal coronary arteries. *Am J Cardiol*. 2015;116:838–844. doi: 10.1016/j.amjcard.2015.06.011
13. Choo EH, Chang K, Lee KY, Lee D, Kim JG, Ahn Y, Kim YJ, Chae SC, Cho MC, Kim CJ, et al. Prognosis and predictors of mortality in patients suffering myocardial infarction with non-obstructive coronary arteries. *J Am Heart Assoc*. 2019;8:e011990. doi: 10.1161/JAHA.119.011990
14. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, Reynolds HR, Geda M, Bueno H, Dziura JD, et al. Presentation, clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO Study. *J Am Heart Assoc*. 2018;7:1–14. doi: 10.1161/JAHA.118.009174
15. Kang WY, Jeong MH, Ahn YK, Kim YH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi DH, et al. Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? *Int J Cardiol*. 2011;146:207–212. doi: 10.1016/j.ijcard.2009.07.001
16. Barr PR, Harrison W, Smyth D, Flynn C, Lee M, Kerr AJ. Myocardial infarction without obstructive coronary artery disease is not a benign condition (ANZACS-QI 10). *Heart Lung Circ*. 2018;27:165–174. doi: 10.1016/j.hlc.2017.02.023
17. Grodzinsky A, Arnold SV, Gosch K, Spertus JA, Foody JM, Beltrame J, Maddox TM, Parashar S, Kosiborod M. Angina frequency after acute myocardial infarction in patients without obstructive coronary artery disease. *Eur Heart J Qual Care Clin Outcomes*. 2015;1:92–99. doi: 10.1093/ehjqcco/qcv014
18. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J*. 2015;36:475–481. doi: 10.1093/eurheartj/ehu469
19. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Camma G, Lanza GA, Crea F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J*. 2018;39:91–98. doi: 10.1093/eurheartj/ehx667
20. Gerbaud E, Arabucki F, Nivet H, Barbey C, Cetran L, Chassaing S, Seguy B, Lesimple A, Cochet H, Montaudon M, et al. OCT and CMR for the diagnosis of patients presenting with MINOCA and suspected epicardial causes. *JACC Cardiovasc Imaging*. 2020;13:2619–2631. doi: 10.1016/j.jcmg.2020.05.045
21. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GBJ, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 2011;124:1414–1425. doi: 10.1161/CIRCULATIONAHA.111.026542
22. Bezerra HG, Costa MA, Guagliumi G, Rollins AM, Simon DI. Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *JACC Cardiovasc Interv*. 2009;2:1035–1046. doi: 10.1016/j.jcin.2009.06.019
23. Ouldzein H, Elbaz M, Roncalli J, Cagnac R, Carrie D, Puel J, Alibelli-Chemarin MJ. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. *Ann Cardiol Angeiol*. 2015;61:20–26. doi: 10.1016/j.ancard.2011.07.011
24. Talebi S, Moreno P, Dominguez AC, Tamis-Holland JE. The imaging toolbox to assess patients with suspected myocardial infarction in the absence of obstructive coronary artery disease (MINOCA). *Curr Cardiol Rep*. 2020;22:134. doi: 10.1007/s11886-020-01379-x
25. Reynolds HR, Maehara A, Kwong RY, Sedlak T, Saw J, Smilowitz NR, Mahmud E, Wei J, Marzo K, Matsumura M, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of myocardial infarction with nonobstructive coronary arteries in women. *Circulation*. 2021;143:624–640. doi: 10.1161/CIRCULATIONAHA.120.052008
26. Iqbal SN, Feit F, Mancini GBJ, Wood D, Patel R, Pena-Sing I, Attubato M, Yatskar L, Slater JN, Hochman JS, et al. Characteristics of plaque disruption by intravascular ultrasound in women presenting with myocardial infarction without obstructive coronary artery disease. *Am Heart J*. 2014;167:715–722. doi: 10.1016/j.ahj.2014.01.011
27. Abdel-Aty H, Zagrosek A, Schulz-Menger J, Taylor AJ, Messroghli D, Kumar A, Gross M, Dietz R, Friedrich MG. Delayed enhancement and

T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation*. 2004;109:2411–2416. doi: 10.1161/01.CIR.0000127428.10985.C6
28. Kim RJ, Albert TS, Wible JH, Elliott MD, Allen JC, Lee JC, Parker M, Napoli A, Judd RM; Gadoversetamide Myocardial Infarction Imaging Investigators. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117:629–637. doi: 10.1161/CIRCULATIONAHA.107.723262
29. Pasupathy S, Tavella R, Beltrame JF. The what, when, who, why, how and where of myocardial infarction with non-obstructive coronary arteries (MINOCA). *Circ J*. 2016;80:11–16. doi: 10.1253/circj.CJ-15-1096
30. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol*. 2009;53:1475–1487. doi: 10.1016/j.jacc.2009.02.007
31. Lurz P, Luecke C, Eitel I, Föhrenbach F, Frank C, Grothoff M, de Waha S, Rommel K-P, Lurz JA, Klingel K, et al. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-Trial. *J Am Coll Cardiol*. 2016;67:1800–1811. doi: 10.1016/j.jacc.2016.02.013
32. Sörensson P, Ekenbäck C, Lundin M, Agewall S, Bacsovics Brolin E, Caidahl K, Cederlund K, Collste O, Daniel M, Jensen J, et al. Early comprehensive cardiovascular magnetic resonance imaging in patients with myocardial infarction with nonobstructive coronary arteries. *JACC Cardiovasc Imaging*. 2021;14:1774–1783. doi: 10.1016/j.jcmg.2021.02.021
33. Pathik B, Raman B, Mohd Amin NH, Mahadavan D, Rajendran S, McGavigan AD, Grover S, Smith E, Mazhar J, Bridgman C, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1146–1152. doi: 10.1093/ehjci/jev289
34. Collste O, Sörensson P, Frick M, Agewall S, Daniel M, Henareh L, Ekenbäck C, Eurenius L, Guiron C, Jernberg T, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. *J Intern Med*. 2013;273:189–196. doi: 10.1111/j.1365-2796.2012.02567.x
35. Tornvall P, Gerbaud E, Behaghel A, Chopard R, Collste O, Laraudogoitia E, Leurent G, Meneveau N, Montaudon M, Perez-David E, et al. Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: a meta-analysis of individual patient data. *Atherosclerosis*. 2015;241:87–91. doi: 10.1016/j.atherosclerosis.2015.04.816
36. Vágó H, Szabó L, Dohy Z, Czimbalmos C, Tóth A, Suhai FI, Bárczi G, Gyarmathy VA, Becker D, Merkely B. Early cardiac magnetic resonance imaging in troponin-positive acute chest pain and non-obstructed coronary arteries. *Heart*. 2020;106:992–1000. doi: 10.1136/heartjnl-2019-316295
37. Pelliccia F, Pepine CJ, Berry C, Camici PG. The role of a comprehensive two-step diagnostic evaluation to unravel the pathophysiology of MINOCA: a review. *Int J Cardiol*. 2021;336:1–7. doi: 10.1016/j.ijcard.2021.05.045
38. Vicente-Ibarra N, Feliu E, Bertomeu-Martínez V, Cano-Vivar P, Carrillo-Sáez P, Morillas P, Ruiz-Nodar JM. Role of cardiovascular magnetic resonance in the prognosis of patients with myocardial infarction with non-obstructive coronary arteries. *J Cardiovasc Magn Reson*. 2021;23:83. doi: 10.1186/s12968-021-00773-w
39. Dastidar AG, Baritussio A, De Garate E, Drobnii Z, Biglino G, Singhal P, Milano EG, Angelini GD, Dorman S, Strange J, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. *JACC Cardiovasc Imaging*. 2019;12:1973–1982.
40. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J*. 2008;155:408–417. doi: 10.1016/j.ahj.2007.11.008
41. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, Francone M, Desch S, Gutberlet M, Strohm O, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy. *JAMA*. 2011;306:277–286. doi: 10.1001/jama.2011.992
42. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, Abbate A. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1955–1971. doi: 10.1016/j.jacc.2018.07.072
43. Vitale C, Rosano GM, Kaski JC. Role of coronary microvascular dysfunction in Takotsubo cardiomyopathy. *Circulation*. 2016;80:299–305. doi: 10.1253/circj.CJ-15-1364
44. Luscher TF, Templin C. Is Takotsubo syndrome a microvascular acute coronary syndrome? Towards a new definition. *Eur Heart J*. 2016;37:2816–2820. doi: 10.1093/eurheartj/ehw057
45. Loffi M, Santangelo A, Kozel M, Kocka V, Budesinsky T, Lisa L, Tousek P. Takotsubo cardiomyopathy: one more angiographic evidence of microvascular dysfunction. *Biomed Res Int*. 2018;2018:5281485. doi: 10.1155/2018/5281485
46. Kobayashi Y, Okura H, Kobayashi Y, Fukuda S, Hirohata A, Yoshida K. Left ventricular myocardial function assessed by three dimensional speckle tracking echocardiography in Takotsubo cardiomyopathy. *Echocardiography*. 2017;34:523–529. doi: 10.1111/echo.13492
47. Lee M. Time course of functional recovery in Takotsubo (stress) cardiomyopathy: a serial speckle tracking echocardiography and electrocardiography study. *J Cardiovasc Imaging*. 2020;28:50–60. doi: 10.4250/jcvi.2019.0083
48. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction. *J Am Coll Cardiol*. 2018;138:e618–e651.
49. Gonzalez JA, Lipinski MJ, Flors L, Shaw PW, Kramer CM, Salerno M. Meta-analysis of diagnostic performance of coronary computed tomography angiography, computed tomography perfusion, and computed tomography-fractional flow reserve in functional myocardial ischemia assessment versus invasive fractional flow reserve. *Am J Cardiol*. 2015;116:1469–1478. doi: 10.1016/j.amjcard.2015.07.078
50. Tweet MS, Gulati R, Williamson EE, Vrtiska TJ, Hayes SN. Multimodality imaging for spontaneous coronary artery dissection in women. *JACC Cardiovasc Imaging*. 2016;9:436–450. doi: 10.1016/j.jcmg.2016.01.009
51. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8:342–358. doi: 10.1016/j.jcct.2014.07.003
52. Torres-Ayala SC, Maldonado J, Bolton JS, Bhalla S. Coronary computed tomography angiography of spontaneous coronary artery dissection: a case report and review of the literature. *Am J Case Rep*. 2015;16:130–135. doi: 10.12659/AJCR.892805
53. Russo V, Marrozzini C, Zompatori M. Spontaneous coronary artery dissection: role of coronary CT angiography. *Heart*. 2013;99:672–673. doi: 10.1136/heartjnl-2012-303215
54. Linde JJ, Kelbæk H, Hansen TF, Sigvardsen PE, Torp-Pederson C, Bech J, Heitmann M, Nielsen OW, Høfsten D, Kühl JT, et al. Coronary CT angiography in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:453–463. doi: 10.1016/j.jacc.2019.12.012
55. Gray AJ, Roobottom C, Smith JE, Goodacre S, Oatey K, Rachel O, Storey RF, Robert LJ, Lewis SE, et al. Rapid Assessment of Potential Ischaemic Heart Disease with CTCA: The RAPID-CCTA trial. A Randomised Trial of CTCA in the Evaluation, Intervention and Outcome Of Adults with Suspected or Confirmed Acute Coronary Syndrome Presenting to the Emergency Department. *Circulation*. 2020;142:e471–472.
56. Achenbach S, Goroll T, Seltmann M, Pflederer T, Anders K, Ropers D, Daniel WG, Uder M, Lell M, Marwan M. Detection of coronary artery stenoses by low-dose, prospectively ECG-triggered, high-pitch spiral coronary CT angiography. *JACC Cardiovasc Imaging*. 2011;4:328–337. doi: 10.1016/j.jcmg.2011.01.012
57. Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, Kramer CM, Min JK, Newby LK, Nixon JV, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. *Circulation*. 2014;130:350–379. doi: 10.1161/CIR.0000000000000061
58. Yasue H, Tkizawa A, Nagao M, Nishida S, Horie M, Kubota J, Omote S, Takaoka K, Okumura K. Long-term prognosis for patients with variant

angina and influential factors. *Circulation*. 1988;78:1–9. doi: 10.1161/01.CIR.78.1.1

59. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation*. 2017;135:1481–1489. doi: 10.1161/CIRCULATIONAHA.116.026336
60. Nordenskjöld AM, Agewall S, Atar D, Baron T, Beltrame J, Bergström O, Erlinge D, Gale CP, López-Pais J, Jernberg T, et al. Randomized evaluation of beta blocker and ACE-inhibitor/angiotensin receptor blocker treatment in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA-BAT): rationale and design. *Am Heart J*. 2021;231:96–104. doi: 10.1016/j.ahj.2020.10.059