



Review article

Clinical presentation and management of myocardial infarction with nonobstructive coronary arteries (MINOCA): A literature review

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ABSTRACT

Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA), as the name implies, is an acute myocardial infarction (MI) in the absence of significant coronary artery obstruction. Diagnosis and management of such cases have been challenging. There are many etiologies of MINOCA including coronary artery spasm, coronary microvascular dysfunction, plaque disruption, spontaneous coronary thrombosis or emboli, spontaneous coronary artery dissection, or cardiomyopathies. In this paper, the pathophysiology, diagnostic work-up, and clinical management for each subtype are described, and an overarching approach on how to evaluate and manage a patient presenting with MINOCA.

1. Introduction

Myocardial infarction with nonobstructive coronary arteries is defined as an acute myocardial infarction (MI) without significant coronary artery obstruction on angiography (>50%) or without specific imaging findings [1]. MINOCA has remained a clinical challenge for physicians. In some cases, patients have been falsely diagnosed with an ST-segment elevation myocardial infarction (STEMI) after angiography failed to find a significant coronary artery thrombosis or stenosis [2]. This puzzling clinical picture led to the first descriptions of MINOCA and established the need for further investigations to elaborate its etiology, diagnostic protocol, and management [3]. So far, many potential etiologies have been suggested as a culprit for MINOCA including coronary artery spasm, coronary microvascular dysfunction, plaque disruption, spontaneous coronary thrombosis or emboli, spontaneous coronary artery dissection or cardiomyopathies. Noncardiac causes such as pulmonary embolism have also been proposed [1, 4]. These conditions can cause transient ischemia of the cardiac tissue and were previously believed to be a more benign form of an acute coronary syndrome (ACS). However, recent literature has found that patients with MINOCA have a

greater risk profile with greater mortality rates than single-vessel obstructive ACS, but less than multi-vessel obstructive ACS [5]. There has been a push by major cardiac societies to draw attention and recognition to MINOCA with the goal to increase its inclusion in differential diagnoses and better ensure appropriate workup and treatment [6]. This review aims to explore the clinical presentation and different causes of MINOCA with a focus on the appropriate diagnostic work-up and management of each.

2. Epidemiology and risk factors

Multiple studies have explored the epidemiology of MINOCA within their population with prevalence found to be between 5-25% of all MI events [6, 7, 8]. The VIRGO study reported that among young adults aged 18–55, women had 5 times greater odds of having MINOCA than men and they had comparable clinical outcomes as those who had myocardial infarction due to coronary artery disease (MI-CAD) at a similar age [7]. It has also been found that black patients were more likely to have MINOCA than MI-CAD [9]. Risk factors are dependent on the underlying etiology of the cause of the MINOCA. Interestingly, it has also been found that

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MINOCA patients are less likely to have traditional risk factors like dyslipidemia, hypertension, diabetes mellitus, family history of MI, and tobacco usage, but were more predisposed to the hypercoagulable state than MI-CAD [7, 10].

3. Presentation

Patients with MINOCA present similarly to those with acute myocardial infarction with obstructive coronary arteries including symptoms of cardiac ischemia and elevated troponins. However, MINOCA patients lack angiographically significant coronary artery obstruction and an immediately clear cause of presentation [11, 12]. They typically present with non-ST segment elevation myocardial infarction (NSTEMI) on ECG [12, 13]. In addition, MINOCA patients are typically younger and more often are women [7]. See supplementary material as an example of presentation.

4. MINOCA subtypes and their underlying pathophysiology

Several pathophysiological mechanisms have been proposed for MINOCA. The fourth universal definition of MINOCA identifies three subtypes including; plaque disruption as type 1, coronary artery spasm, microvascular dysfunction, spontaneous coronary artery dissection and coronary embolism as type 2 and finally type 3 which is defined as sudden cardiac death in patients with symptoms or ECG signs of myocardial ischemia or with myocardial infarction detection at autopsy examination [14]. Simplistically, MINOCA mechanisms can be thought of as malfunctions of epicardial vessels and/or coronary microcirculation. Epicardial causes include coronary artery spasms or transient and partial thrombosis at the site of a nonobstructive plaque. Microvascular causes include coronary microvascular dysfunctions like Cardiac Syndrome X and angina pectoris with normal coronary arteries. This does not provide an exhaustive list of possible causes; other etiologies include spontaneous coronary artery dissection, coronary artery embolism, or even pulmonary embolism [15]. It should be noted that other pathologies, particularly stress-induced cardiomyopathy (Takotsubo syndrome) and myocarditis, can mimic MI/MINOCA. While excluded from the definition of MINOCA, these syndromes should remain on the differential when evaluating patients with presentations suggesting MI/MINOCA.

4.1. Type I MI

4.1.1. Coronary plaque disruption

Coronary plaque disruption is an umbrella term for a collection of conditions involving coronary plaques. It encompasses plaque rupture, plaque erosion, and calcific nodules. The pathophysiology of these conditions is similar to that of myocardial infarction with obstructive coronary artery disease; however, to be considered MINOCA, the obstruction must be less than 50% and the transient and partial thrombosis at the site of the non-obstructive plaque must be followed by subsequent spontaneous fibrinolysis of the clot [16]. These atherosclerotic plaques extend outwards rather than intruding into the arterial lumen [17]. Therefore, they are easily overlooked on coronary angiography. Plaque rupture, the most common culprit of coronary thrombosis, occurs when there is damage to the fibrous cap and exposure of the plaque's internal thrombogenic core to the blood vessel lumen [18, 19, 20, 21]. A thrombus can be formed over the damaged plaque and can cause an acute myocardial infarction. But just as quickly as the occlusion occurs, it can rapidly disappear with rapid fibrinolytic activity, which can explain why upon angiography, there is no evidence of occlusion. Calcific nodules are another component of coronary plaque disruption and are found invading the lumen through the ruptured fibrous cap. Plaque erosions and their mechanisms are currently not completely defined [19]. Both mechanisms for the infarction are similar to plaque rupture.

4.2. Type II MI

4.2.1. Spontaneous coronary artery dissection

In spontaneous coronary artery dissection (SCAD), there is an interruption in coronary vessel blood flow from the separation of the vascular wall layers. The dissection introduces a false lumen that becomes an intramural hematoma, which expands into the coronary vessel lumen and obstructs myocardial perfusion. Although the precise inciting factors remain unknown, it is theorized that an intrinsic vasculopathy may predispose to SCAD, which then precipitates under a catecholamine surge from stressors such as physical exertion or sympathomimetic drugs [22, 23, 24]. This theory is supported by an association between SCAD and other vascular diseases, particularly fibromuscular dysplasia [24]. Although SCAD is an uncommon cause of acute MI overall, it is a relatively common mechanism of acute MI in women under age 50 [25, 26]. SCAD should be considered in younger women with an unexplained ACS or sudden cardiac death.

4.2.2. Coronary artery spasm

Also known as vasospastic angina and previously known as Prinzmetal or variant angina, coronary artery spasms are characterized by transient episodes of resting angina that is attributed to focal or diffuse epicardial coronary artery vasospasms resulting in a high-grade obstruction [27]. In the epicardial spasm subtype, vascular smooth muscle hyperactivity causes prolonged vasospastic episodes and can lead to myocardial ischemia and infarction with transient ST-segment elevations in the absence of coronary artery obstruction [28]. Animal and clinical studies that have tried to elucidate the pathophysiologic mechanism have shown that these spasms are not provoked by a single receptor pathway, and receptor antagonism with Ketanserin or Prazosin does not inhibit spasms [29, 30, 31, 32]. However, studies have shown that smooth muscle contractility inhibition with non-receptor antagonists such as nitrates and calcium channel blockers is effective. This is illustrated in studies showing the underlying mechanism of these spasms is due to increased calcium sensitivity of the vascular myosin light chain mediated by enhanced Rho kinase and enhanced phospholipase C activity [6, 33, 34, 35]. Increased vagal tone and hyperreactivity to sympathetic stimulation have also been linked to vasospastic angina. This hypothesis has been supported by the observation that surgical sympathetic denervation may be an effective therapy in medically refractory cases of coronary artery spasms [36, 37]. A major risk factor for developing these spasms is cigarette smoking and some possible triggers include ephedrine-based medications, cocaine, marijuana, alcohol, butane, sumatriptan, amphetamines, percutaneous coronary intervention, food-borne botulism, and magnesium deficiency [5, 7, 38, 39, 40, 41]. The long-term prognosis is generally good for these patients and five-year survival rates may be as high as 94 percent [42].

4.2.3. Myocardial bridging

Myocardial bridging (MB) is a congenital variant where epicardial coronary arteries dive into the myocardium and undergo dynamic compression during systole. While initially thought to be a benign condition, it has more recently been investigated as a cause of angina and MINOCA [43]. In this study the presence of coronary spasms in patients with MB was examined, as well as its effect on outcome and prognosis. MB was present in approximately 17% of patients who underwent coronary angiogram for a suspected myocardial infarction [44]. Previous studies have reported that the presence of microvascular dysfunction plays a major role in the mechanism of angina and symptoms in patients with MB [45]. In their longitudinal study, the Montone RA *et al* group found MB was an independent predictor of MINOCA and detected the presence of coronary artery spasm in 21% of patients with MB using a provocative acetylcholine test. The MB variant was associated with worse outcomes including higher rates of major adverse cardiac events and angina recurrence, as well as lower quality of life. These findings were even more pronounced in the group with a positive coronary spasm test.

The utility of invasive provocative tests was reiterated, given their ability to detect the presence of vasomotor disorders with implications for improving outcomes and determining appropriate therapy regimens [44].

4.2.4. Coronary microvascular dysfunction

Also known as cardiac syndrome X, microvascular angina (MVA) is a coronary microvascular dysfunction characterized by transient myocardial ischemia, as seen by ST-segment changes, in the absence of obstructive coronary artery disease and epicardial spasms [18]. The pathogenesis of this condition is believed to be due to coronary microvascular oversensitivity to vasoconstrictors and lower vasodilator capacity [19]. The dysfunction affects only the smaller caliber coronary vessels (less than 500 μm) and it is characterized by reduced coronary flow reserve (CFR) [46]. Coronary microvascular spasms, different from focal epicardial coronary artery spasms, have also been hypothesized to contribute to MVA. This can be detected during angiographic studies in patients with chest pain despite angiographically normal coronary arteries using intracoronary acetylcholine testing [47].

4.2.5. Coronary thromboembolism

MINOCA can also result from coronary thromboembolism (CE) that affects microcirculation. Hypercoagulable disorders can predispose patients to the development of thrombosis such as protein C and S deficiency, factor V Leiden, elevated factor VIII or von Willebrand factor, or malignancy with myeloproliferative, heparin-induced thrombocytopenia, thrombocytopenic purpura and antiphospholipid syndrome. MI attributed to coronary thromboembolism is more common in younger women, and prevalence also varies with race and ethnicity, especially those that are associated with hypercoagulable disorders [48, 49, 50].

5. MINOCA work-up and clinical treatment regimens

Because of the relatively nonspecific presentation of MINOCA, other diagnoses must be ruled out first. For example, NSTEMI, sepsis, pulmonary embolism, cardiac contusions, and other non-cardiac causes of elevated troponins can present similarly to MINOCA [11, 12, 13]. Because each etiology has unique pathophysiology, work-up, and treatment, it is imperative to use a systematic approach to evaluate alternative diagnoses. When a patient presents with signs and symptoms that suggest ACS, angiography is one of the first diagnostic steps. If there are findings of obstructions greater than 50%, the infarct is most likely due to obstructive coronary artery disease. If coronary arteries are widely patent or if obstructions are less than 50%, angiography results should be revisited. If it is confirmed that there is still no occlusion greater than 50%, other non-cardiac causes such as sepsis, pulmonary embolism, amyloidosis, sarcoidosis, blunt chest trauma, or gastrointestinal causes should be ruled out. In many clinical situations, the next step after angiography includes transthoracic Doppler echocardiography (TTDE) which is readily available at most institutions. TTDE can narrow the differential, and can guide further investigations and interventions. Once it is determined that obstructive CAD has been excluded or cannot fully account for the patient's myocardial ischemia, cardiac magnetic resonance imaging (CMR) should be pursued, if available. Finally, vasomotor coronary disorders should be considered and further evaluated via coronary provocative tests [51]. It should be noted that clinical judgment and a personalized approach to diagnosis is of considerable importance in evaluating a patient with MINOCA [52].

CMR is a particularly important diagnostic tool when MINOCA is suspected [53]. CMR has emerged as the gold standard for noninvasive assessment of the heart due to its safety, accuracy, ability to characterize the myocardium, and inter-observer consistency. This was also reiterated by the European Society of Cardiology (ESC) [1, 54]. CMR can help establish the diagnosis of MINOCA by ruling out conditions with similar presentations, including stress-induced, hypertrophic, or dilated cardiomyopathies, myocarditis, and MI-CAD [55]. It has been suggested that

CMR can identify the underlying etiology in nearly two thirds of MINOCA cases, as well as provide prognostic and stratification data that can change therapeutic strategies in as many as half of cases [56, 57]. CMR can support the diagnosis of infarct but the technology is not readily available in every center; thus, clinical judgment is still crucial for further workup. See supplementary material as an example of diagnostic work-up.

Once it is determined that MINOCA is the most likely diagnosis, coronary vasomotor disorders should be further evaluated using provocative spasm testing for confirmation. Provocative spasm testing with acetylcholine or ergonovine is a cornerstone in the approach to MINOCA given its high diagnostic yield. This diagnostic study takes advantage of the vasoconstricting effects of acetylcholine or ergonovine to determine if coronary artery spasms result. This allows for simultaneous assessment of epicardial vessels as well as microvascular dysfunction. Side effects and adverse outcomes of the test include arrhythmias with an incidence of 6.8% [58]. Other rare (<0.5%) but serious consequences of provocative spasm testing include coronary artery dissection, coronary spasm refractory to nitrate administration, and cardiogenic shock. However, such testing is relatively safe, particularly when initiated within 48 hours of an admission for MINOCA [59].

If clinical judgment favors SCAD or plaque disruption over vasomotor disorders, other imaging modalities are available. Invasive imaging like intravascular ultrasound (IVUS) and optical coherence tomography (OCT) is useful in visualizing SCAD and plaque disruption [60]. However, caution should be applied when considering these invasive imaging modalities due to iatrogenic risks such as further propagating intimal dissections or disrupting plaques. Due to their inherent risk profiles, invasive imaging should only be performed if clinically indicated and if doing so may change the therapeutic course [53, 60].

In general, MINOCA treatment has some similarities to MI-CAD treatment, but some notable differences as well. Unlike MI-CAD, only a few studies have tried to examine the associations between pharmacological therapy and long-term cardiovascular events in MINOCA patients. Lindahl B *et al* conducted an observational study utilizing the SWEDEHEART registry to examine pharmacologic options to decrease major adverse cardiac events (MACE). Examples of MACE include all-cause mortality, strokes, hospitalization for MI and heart failure. This study reported lower rates of MACE with angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and statins, and potential benefits using beta-blockers. Notably, Lindahl B. *et al* did not report any benefit of using dual antiplatelet therapy [61].

6. MI-CAD

While MI-CAD is not a subtype of MINOCA, it is the first condition one should consider and thus warrants some discussion. MI-CAD work-up begins with confirming the presence of myocardial ischemia or infarct based on the MI criteria. This involves obtaining an EKG ideally within 10 minutes of arrival to the ED [62]. These MI criteria include symptoms of myocardial ischemia, new significant ST or T wave changes or new left bundle branch block on EKG, development of pathologic Q-waves on EKG, imaging evidence of new loss of viable myocardium or regional wall motion abnormality, and identification of a coronary thrombus. Cardiac biomarkers including troponin should be obtained at the time of presentation as well. The next step is always to obtain imaging via coronary angiography. At this point, MI-CAD can be differentiated from MINOCA. Angiographic diagnosis of MI-CAD requires the presence of >50% vessel occlusion in any potential infarct-related artery. On the other hand, MINOCA requires the presence of the same MI criteria, but without the presence of >50% vessel occlusion on angiography. At the same time, no specific alternate diagnoses such as sepsis, pulmonary embolism, etc. can be made to explain the clinical picture [62].

The initial management targeted at reducing ischemia and pain involves nitrates, beta-blockers, calcium channel blockers if beta-blockers cannot be tolerated due to bronchospasm, and supplemental oxygen.

Morphine can also be used with clinical judgment to reduce pain and anxiety, thereby decreasing preload, and through vasodilation. Additionally, antiplatelet therapy with aspirin should be started immediately as it is the accepted treatment that can stabilize plaque and limit infarct progression. A P2Y12 inhibitor may be added to ASA but the appropriate timing remains controversial. A high-intensity statin and anticoagulant, most often heparin, should be started as well, especially since immediate angiography is not planned or feasible. Reperfusion therapy should be started promptly to rescue cardiac tissue and reduce mortality. Emergent treatment with percutaneous coronary intervention and fibrinolysis should be immediately considered. Coronary bypass grafting can also be considered for severe coronary artery disease. Long-term medical management consists of dual antiplatelet therapy, statins, ACEIs or ARBs, and beta-blockers [63].

7. Coronary plaque disruption

These episodes of transient myocardial infarction events are labeled as MINOCA because angiography alone is of limited utility for the purpose of elucidating plaque-related thrombosis as a cause of infarction. This is due to its low resolution as well as the fact that it does not examine the walls of the vessel. In these instances, intracoronary imaging modalities such as IVUS and OCT can be used during cardiac catheterization to elucidate whether the cardiac presentation was secondary to plaque disruption. MRI imaging within the following week of the event can also be of diagnostic value and can be used to guide management to prevent future events. In a study published in the European Heart Journal, Reynolds *et al* studied a group of women with <50% stenosis on angiograms who presented with a myocardial ischemic event evident by either troponin elevation or ST-segment elevation. Of the 42 women who underwent IVUS, 16 (38%) demonstrated imaging changes indicative of coronary plaque disruption. There were 44 subjects who underwent cardiac magnetic resonance imaging within 1 week in which 26 (59%) demonstrated either late gadolinium enhancement (LGE) or T2 signal hyperintensity indicating edema and evidence of changes indicating coronary plaque disruption [64]. OCT offers the highest resolution imaging. According to the Texas Heart Institute, OCT allows clinicians to see the inside of an artery in 10 times more detail than if they were using intravascular ultrasound. Although this is a fairly novel technology, its use in combination with angiography during cardiac catheterization can be incredibly useful for allowing cardiologists to clearly visualize the plaque inside an artery, evaluate the extent of intraluminal clot or thrombosis, and take precise measurements before and after placing stents. Long-term therapy for patients presenting with MINOCA secondary to coronary plaque disruption will be treated similarly to patients presenting with ACS as the pathophysiology of both conditions is the same. The need for angioplasty and stent placement is unnecessary as there will be no significant acute coronary blockage found on angiography. However, the patient should be discharged on aspirin, a platelet P2Y12 receptor blocker, a beta-blocker, and a statin in order to prevent future events [61]. In particular, long-term high-intensity statin therapy is of significant importance at increasing the fibrous-cap thickness, stabilizing the plaque, and preventing rupture [65].

8. Spontaneous coronary artery dissection

Diagnosis of SCAD requires imaging to evaluate the coronary vascular walls. Angiography is generally the first line of testing for patients with ACS, and is widely available; however, the 2-dimensional view has limited ability to visualize the arterial wall. Intracoronary imaging to visualize the arterial wall can be achieved with OCT or IVUS. These modalities are not as widely available as angiography, can be costly, and confer additional risks such as the extension of the dissection. This limited availability of appropriate imaging may contribute to the likely under-reported prevalence of SCAD. Given its superior resolution, OCT is considered the gold standard for SCAD imaging and diagnosis [66].

Cardiac CT angiography and cardiac MRI have limited ability to visualize the small coronary vessels or the subtle difference between normal and dissected vessels and are generally not recommended for SCAD diagnosis. Given the strong association with fibromuscular dysplasia (FMD), patients who present with SCAD should be considered for further screening to evaluate underlying FMD. This can be accomplished either during the initial angiography or by non-invasive CTA by noting the renal and iliac arteries for signs of FMD [24, 67, 68].

Currently, there are no randomized trials to direct medical therapy for SCAD, and treatment recommendations are largely based on expert opinion [69, 70, 71]. Conservative therapy is the preferred management of SCAD, as most cases spontaneously resolve [24, 71, 72, 73, 74]. Intimal tears can be prothrombotic, thus empiric dual antiplatelet therapy (DAPT) with aspirin and clopidogrel can be used prophylactically [75]. Conservative management also includes beta-blockers which may reduce additional arterial wall stress, as seen with aortic dissection [76]. Other therapies that are often considered but of uncertain therapeutic value are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins or other cholesterol-lowering medications. Statins may be beneficial in patients with pre-existing dyslipidemia, but to an unclear degree [77]. Patients with ongoing ischemia, hemodynamic instability, or left main dissection, should be considered for revascularization, noting that PCI has high failure rates for SCAD and CABG should be reserved for critically ill patients with extensive dissections of proximal arteries [22, 24, 73, 74].

9. Coronary artery spasm

Coronary artery spasm diagnosis is made based upon three components: nitrate responsive angina, transient ischemic electrocardiogram (ECG) changes in the absence of obvious causes for increased myocardial oxygen demand, and angiographic evidence of coronary artery spasm. An acute episode is often treated with sublingual nitroglycerin which decreases both the duration of symptoms and ischemia. However, most acute episodes will resolve on their own. Long-term treatment for preventing future episodes is often managed with calcium channel blockers as first-line therapy or long-acting nitrates in refractory cases [78, 79]. Lifestyle changes such as smoking cessation will also lead to a significant decrease in the frequency of episodes.

10. Coronary microvascular dysfunction

The diagnostic evaluation specific for MVA usually occurs after coronary angiography has found that chest pain is not likely due to obstructive epicardial coronary artery disease. Definitive diagnosis can be made by fulfilling four criteria proposed by the Coronary Vasomotion Disorders International Study Group (COVADIS). In short, diagnosis is established based upon symptoms suggestive of myocardial ischemia in the absence of obstructive CAD associated with objective evidence of myocardial ischemia and impaired coronary microvascular function (Table 1) [20].

To evaluate for MVA during coronary angiography when no coronary stenosis is appreciated, the physician can perform an acetylcholine test followed by CFR measurements. During an acetylcholine test, incremental doses of intracoronary acetylcholine are administered over three minutes until a response is produced or the target dose is reached. If anginal symptoms or ischemic ECG changes are observed in the absence of epicardial coronary spasms (<75% diameter reduction) then the patient is considered to have MVA [20]. Patients who have a negative response then will be further evaluated by measuring the CFR. CFR is measured during invasive coronary angiography using a Doppler flow wire to measure coronary blood velocity reserve [80, 81]. It is used to express the degree of resistance to blood flow within the microcirculation when no significant epicardial coronary obstruction is appreciated. CFR is the magnitude of increase in coronary flow (per unit of time) that can be achieved between basal coronary perfusion to maximum coronary

Table 1. Diagnostic criteria for microvascular angina.

Criteria	Evidence	Diagnostic Factors
1	Symptoms of myocardial ischemia	Effort and/or rest at angina Angina equivalents (i.e., dyspnea)
2	Absence of CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA Invasive coronary angiography
3	Objective evidence of myocardial ischemia	Ischemic changes during an episode of chest pain Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4	Evidence of impaired coronary microvascular function	Impaired coronary flow reserve (cut-off <2.0) Abnormal coronary microvascular resistance indices (e.g., IMR >25) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing Coronary slow phenomenon, defined as TIMI frame count >25

Definitive MVA is only diagnosed if all four criteria are present.

CAD = coronary artery disease; CTA = coronary computed tomographic angiography; ECG = electrocardiogram; FFR = fractional flow reserve; IMR = index of microcirculatory resistance; TIMI = thrombolysis in myocardial infarction.

vasodilation. It is expressed as the ratio of blood flow during maximal hyperemia, measured after infusion of a coronary vasodilator such as adenosine, to blood flow at rest. Maximal coronary blood flow must be at least 2.5 times greater than the resting blood flow and values below 2.5 are indicative of coronary microvascular dysfunction [82]. If patients are unable to undergo the invasive tests described above or do not have a clear diagnosis following invasive evaluation then the patient can be further worked up post angiography with non-invasive tests such as CT fractional flow reserve (not widely available), positron emission tomography–CFR, CMR during maximal hyperemia induced by administration of vasodilators, and coronary flow velocity measurements using transthoracic Doppler echocardiography [83, 84, 85, 86]. In a study by DeVita et al, it was seen that patients with MINOCA exhibit significant coronary artery dysfunction with both increased constrictor reactivity and reduced microvascular dilator function with both findings persisting at the 12 months follow up [87]. To relieve acute episodes of angina, patients should be prescribed sublingual nitroglycerin [38]. For long-term prevention, beta-blockers seem to be most effective in reducing the frequency and severity of angina and in improving exercise tolerance; however, definitive controlled trials are not available [21]. Calcium channel blockers have also been found to be effective in many studies [21, 88, 89].

11. Coronary thromboembolism

The criteria for the diagnosis of CE include three major and three minor criteria which are then scored and weighted to differentiate between definite and probable coronary thromboembolism. The major criteria include angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic component, concomitant coronary artery embolization at multiple sites, and concomitant systemic embolization without left ventricular thrombus attributable to acute myocardial infarction. The minor criteria include <25% stenosis, evidence of an embolic source based on transthoracic echocardiography, transesophageal echocardiography, computed tomography, or MRI, and presence of embolic risk factors [90]. Work-up should include TTE, TOE, or bubble contrast echocardiography to uncover cardiac sources of emboli and coronary angiography to detect possible distal branch embolism. IVUS and OCT can also be used to evaluate whether the aneurysm

is a potential source of thrombus. Additional work-up measures should include thrombophilia screening with factor V Leiden, prothrombin 20210A, factor VIII, proteins C and S, antithrombin, lupus anticoagulant, antiphospholipid antibodies [90, 91]. The treatment of CE should be individualized. Cases involving atrial septal defects require percutaneous or surgical closure. Antiplatelets or anticoagulation therapy can be considered for the prevention of left-sided origin coronary embolism [90, 91].

12. Unknown etiology

Diagnosing MINOCA of unknown etiology is by exclusion. CMR is a powerful imaging modality that oftentimes will elucidate the cause of MINOCA. It has been reported that upon CMR imaging, as low as 8% of patients with MINOCA do not have abnormal findings [91]. This may be due to very little cardiac myonecrosis that is undetectable on CMR or that the necrosis occurs diffusely throughout the myocardial tissue without any concentrated region of cell death [91]. After normal findings on CMR, provocative tests and invasive coronary vascular imaging should be done to further assess for vasospasms, SCAD, coronary microemboli or thrombi, and plaque disruption (Figure 1). Interestingly, there has been a case of fulminant immune-mediated necrotizing myopathy (IMNM) mimicking MINOCA [92]. In summary, the patient who was recently started on adalimumab presented with chest pain and significantly elevated troponin T levels. Upon angiography and CMR imaging, the patient was found to have unobstructed coronary and unremarkable cardiac findings. The authors then investigated the left shoulder on MRI and found edema and muscular enhancements indicative of acute myositis. The patient also had elevated creatine kinase that was of skeletal muscle origin and was positive for anti-Scl-70 antibodies. It may be wise to explore extracardiac etiologies such as IMNM in patients suspected to have MINOCA of unknown etiology. Because there is so little data available and the population is poorly defined, there are currently no recommendations for MINOCA of unknown etiology, but aspirin and statins have been suggested to be potential routine treatments [91, 93]. The latest European Society of Cardiology (ESC) guidelines state that secondary prevention drugs should be considered if the etiology of MINOCA remains unknown, although the benefit from standard therapy is uncertain [1]. Only a few studies have tried to examine the impact of pharmacological therapy on long-term cardiovascular events in patients with MINOCA of unknown etiology and have described conflicting results. A recent retrospective multicenter cohort study in Italy found that standard therapy for secondary prevention of MINOCA may not be beneficial, and may even be detrimental in some subgroups. During a median follow-up of 8.5 years, beta-blockers demonstrated a significant reduction of MACE whereas aspirin was found to be significantly associated with an increased risk of MACE [94]. Conversely, Lindahl. B et al, concluded there was a clear benefit with statins, ACE inhibitors and ARBs, and a potential benefit of beta-blockers in decreasing MACE in patients with MINOCA [61].

13. Prognosis

It was previously accepted that patients with MINOCA have a better prognosis than those with obstructive coronary artery disease. However, long-term outcomes for MINOCA patients are conflicting. Part of this discrepancy may be due to the inconsistent labeling of other conditions under the umbrella MINOCA, particularly stress cardiomyopathies and myocarditis. The inclusion of such conditions obfuscates the true prognostic factors for MINOCA and should be considered before determining the patient's outcome. With these caveats in mind, MINOCA has been associated with lower in-hospital mortality and lower all-cause mortality at 12 months when compared to MI with obstructive CAD [3, 95]. Conversely, MINOCA patients suffered greater all-cause mortality at 12 months compared to patients with NSTEMI and CAD, with a higher rate of non-cardiac deaths. This study also indicated that MINOCA patients

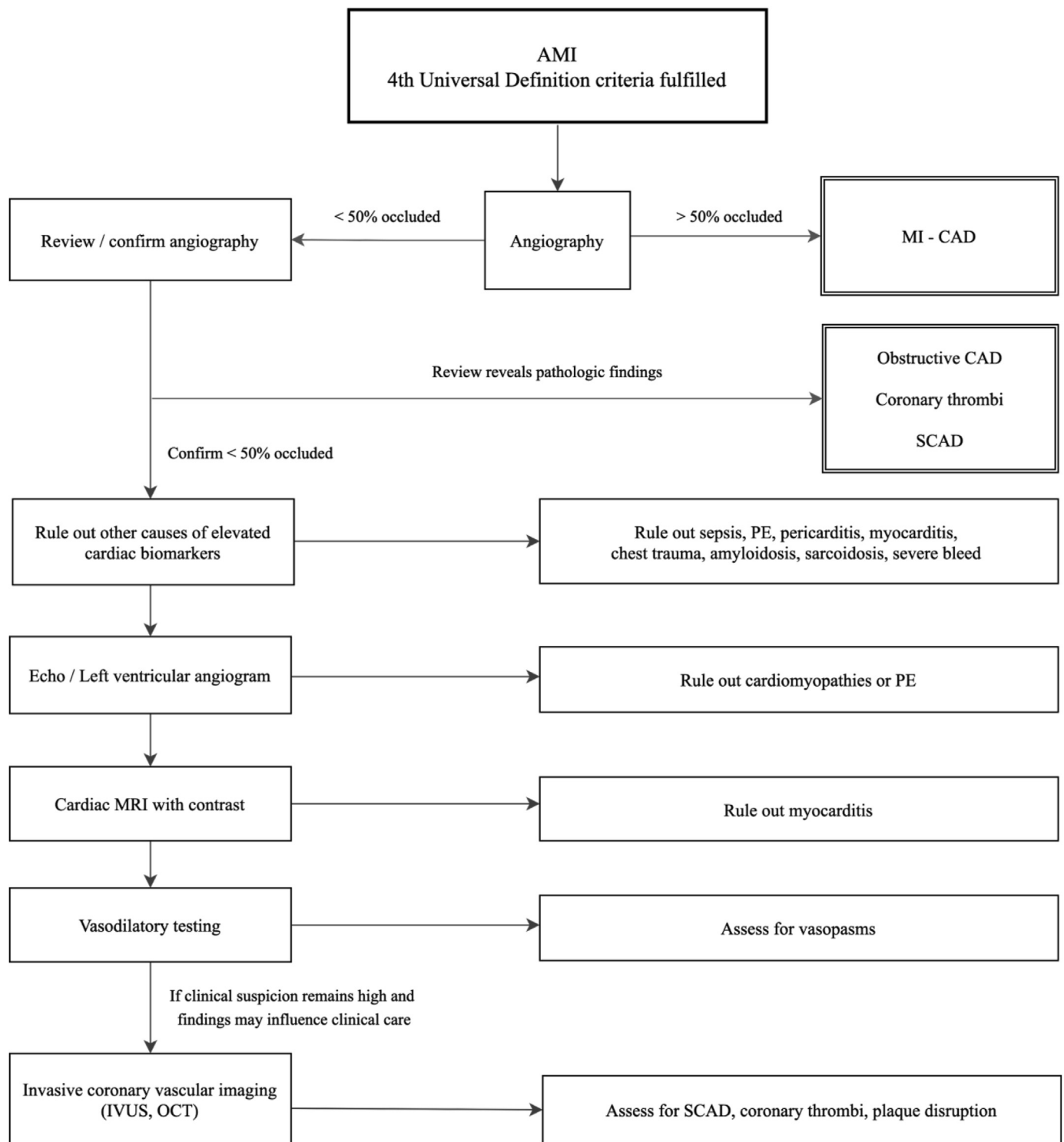


Figure 1. MINOCA algorithm.

experienced lower rates of recurrent MI and fewer revascularization interventions than NSTEMI [96]. Further, MINOCA was implicated in 1–10% of all causes of sudden cardiac death underscoring that it is an uncommon, but important cause of cardiac death [97].

Studies implicating high mortality rates may be explained, in part, by the presence of high-risk epicardial and microvascular MINOCA subsets. Unstable plaque ruptures are considered a high-risk subtype of epicardial mechanism, with worse outcomes compared to the presence of a fibrous cap [98]. Patients with epicardial vasospasm and abnormal response to

ergonovine or acetylcholine tests have also been associated with worse outcomes in quality of life, all-cause mortality, cardiac death, and repeat hospitalization for ACS [99]. In contrast, microvascular spasms generally have a good prognosis, although up to 36% of patients experience persistent angina symptoms despite the use of calcium channel blockers [100]. He *et al.* studied the effects of exercise in patients with MINOCA and found that there was a significant reduction in all-cause mortality and major adverse cardiac events in patients who followed a home-based exercise training program. The study suggests that exercising on the

treadmill or indoor bicycle three times a week can be very effective in maintaining and improving cardiac health in patients with MINOCA [101]. Guidelines for secondary therapies for MINOCA have not been assessed in randomized trials and studies of routine clinical practice suggest that therapies vary widely. Nordenskjöld *et al.* are currently evaluating the effectiveness of beta-blockers and ACE inhibitors/angiotensin receptor blockers in patients with MINOCA [102].

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