Myocardial Infarction Without Obstructive Coronary Artery Disease (MINOCA): A Practical Guide for Clinicians

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Abstract: Myocardial infarction without obstructive coronary artery disease (MINOCA) is defined by the evidence of spontaneous acute myocardial infarction (MI) and angiographic exclusion of coronary stenoses ≥50% in any potential infarct related artery, after having ruled out other clinically overt causes for the acute presentation. The introduction of this new concept was meant to encourage discovery of putative pathophysiological mechanisms and development of specific therapeutic measures. In recent years, we have witnessed significant advances in the fields of epidemiology, pathophysiology, diagnosis, prognosis estimation and therapeutics of MINOCA. So far, however, the definition of MINOCA has been rather heterogeneous since specific cardiac conditions such as myocarditis and Takotsubo syndrome have often been included, generating conflicting results. In this review, we summarize the current state-of-the-art in the

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expanding MINOCA field and propose a comprehensive stepwise approach for the rational diagnostic assessment of these challenging patients. Our aim is to provide clinicians with an "Ariadne's thread" according to the recent fourth universal definition of MI in order to not get lost in MINOCA's labyrinth. (Curr Probl Cardiol 2021;46:100761.)

Introduction

The observation that coronary artery obstruction plays a pivotal role in the pathophysiology of myocardial infarction (MI) was first reported in English in 1912 by James Herrick.[1] Studies conducted in the 1980s showed a very high prevalence of obstructive atherosclerosis in patients undergoing coronary arteriography (CA) within the first few hours of both transmural and nontransmural MI, with a remarkable rate of total coronary occlusion in the former subset.[2] Nonetheless, even in these early reports, it was recognized that no significant coronary artery stenosis can be found in a substantial minority of patients with a clinical picture consistent with MI undergoing CA. In the past, these patients were considered to have "false positive" diagnoses of MI.[3]

In 2013, the term myocardial infarction without obstructive coronary artery disease (MINOCA), an acronym to indicate MI without obstructive coronary artery disease (CAD), was coined.[4] The introduction of this novel concept was meant to fill a gap in knowledge and encourage discovery of putative pathophysiological mechanisms, in order to develop specific management options.[4] In the last few years, the MINOCA concept has given fresh impetus to basic and clinical research in the field of acute coronary syndromes (ACS).

Definition

In 2016, an international working group first proposed diagnostic criteria for MINOCA (Table 1).[5] The key-points included criteria for acute MI (defined as a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile of upper reference limit plus corroborative clinical evidence of MI), documentation of coronary stenosis $<50\%$ in any potential infarct related artery by CA, and exclusion of specific overt causes for the clinical presentation (Table 1).[5]

More recently, the updated fourth universal definition of MI stressed the concept that MI, and therefore MINOCA, should only be diagnosed

Table 1. Diagnostic criteria for myocardial infarction without obstructive coronary artery disease (MINOCA)

1. Acute myocardial infarction according to the fourth universal definition of myocardial infarction
   - Positive cTn assay: detection of rise and/or fall in cTn serial levels, with at least one value above the 99th percentile upper reference limit
   - Corroborative clinical evidence of acute myocardial ischemia as evidenced by at least one of the following:
     - Symptoms of myocardial ischemia
     - New or presumed new significant ST-T changes or new LBBB
     - Development of pathological Q waves
     - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
     - Intracoronary thrombus evident on angiography or at autopsy
2. Non-obstructive coronary lesions on angiography
   - Absence of any coronary artery stenosis ≥50% in any infarct related artery
     This includes patients with:
     - Normal-appearing coronary arteries (no stenosis > 30%)
     - Mild coronary atheromatosis (stenosis >30% but <50%)
3. Absence of other specific causes for the acute presentation

Abbreviations: cTn, cardiac troponin; LBBB, left bundle branch block.
Adapted from Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017; 38(3):143-153 and Tamis-Holland JE, Jneid H, Reynolds HR, 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(18):e891-e908.*

in the presence of clinical, electrocardiographic and/or imaging evidence of ischemia, in order to distinguish acute MI from other causes of acute myocardial injury, such as myocarditis or takotsubo syndrome, which are well distinct and specific entities.[6]

Moreover, latest European guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, clearly state that, by consensus, the current criteria for the MINOCA definition now excludes myocarditis and Takotsubo syndrome from the final diagnosis of MINOCA.[7]

Accordingly, physicians should consider MINOCA a working diagnosis, for which cardiac troponins and CA are important first steps, but additional − and often expensive − tests may be required in order to elucidate the underlying mechanism(s).[5]

Epidemiology

The heterogeneous definitions of obstructive CAD adopted in published series produced substantial variability in the reported prevalence of MINOCA, which could reasonably represent 2% to 6% of all MIs.[8,9]

As compared to MI due to obstructive CAD (MI-CAD), female gender is over-represented in MINOCA, as women are affected in up to 50% of cases, more often in the premenopausal period.[8,9] Furthermore, the average age at presentation (51-59 years) is slightly lower than MI-CAD,[10,11] ethnic minorities (black, Hispanic, Maori, and Pacific) are more commonly affected,[10] and the burden of traditional cardiovascular risk factors appears to be lower.[8,10] Although rare, hypercoagulable states are found more frequently in MINOCA than in MI-CAD.[8,10]

The electrocardiogram (ECG) upon presentation can show ST-segment-elevation in approximately one-third of cases, but in most cases T wave inversion, ST-segment depression or normal ECG findings are observed.[8] Troponin levels are elevated by definition, although they appear to be lower in MINOCA than in MI-CAD.[8,10]

Clinical profiling of MINOCA in order to find a subgroup of ACS patients most likely to have nonobstructed coronary arteries on the basis of clinical presentation and, therefore, to obviate the need for CA, is an interesting topic that still awaits to be fully elucidated.[8] Thus far, however, identification of MINOCA patients relies on angiographic data.[5,10]

Pathophysiology and specific diagnostic investigations

MINOCA encompasses a wide spectrum of conditions. Recognition of pathophysiological mechanisms behind each of these clinical entities is key to successful management of patients. By applying the fourth universal definition of MI, MINOCA could be classified in 3 categories: type 1, type 2, and type 3 (Fig 1).[6]

Type 1 MINOCA

As for type 1 MI-CAD, the main feature of type 1 MINOCA is the presence of atherothrombosis secondary to plaque disruption,[6] which encompasses plaque rupture (PR), plaque erosion (PE) and calcified nodule.[12,13]

PR is the most common form of plaque disruption and is defined by the presence of a tear or gap in the fibrous cap of a lipid-rich plaque, with a necrotic and thrombogenic core.[12,13] On the other hand, PE is typified by mural thrombosis overlying an unruptured plaque rich in proteoglycans and smooth muscle cells, with minimal inflammation, usually accompanied by loss of endothelial lining underneath the thrombus.[12,13] The calcified nodule is a less frequent atherothrombotic lesion characterized by

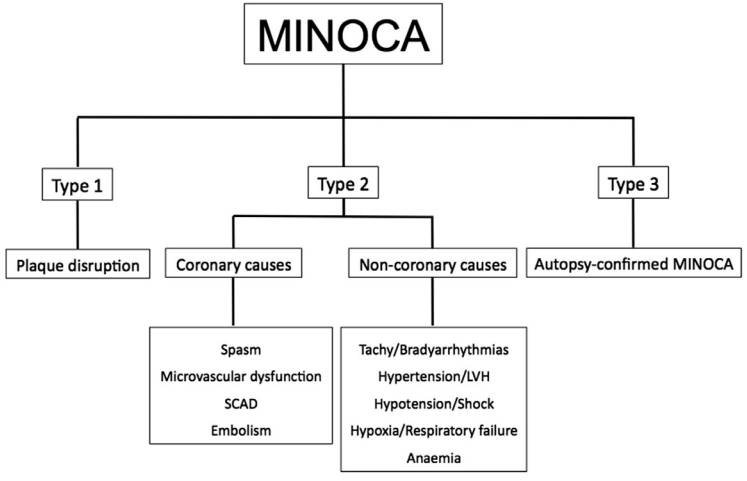

FIG 1. Classification of myocardial infarction without obstructive coronary artery disease (MINOCA) according to the IV universal definition of myocardial infarction.

disruption of the fibrous cap overlying or close to a calcified plaque with protruding calcifications.[12,13]

There are several putative mechanisms by which plaque disruption may be observed in the absence of obstructive angiographic lesions.[6] Spontaneous thrombus recanalization is an important potential explanation, which may be facilitated by use of potent antithrombotic agents in the modern era and longer delays between initial symptoms and CA.[6,12] Furthermore, plaque disruption results in exposition of the subendothelium to platelets, which upon activation can release potent vasoconstricting substances, producing a dramatic and transitory loss of vessel patency.[6,12] Finally, distal embolization of thrombotic debris can occur.[6,12]

Angiographic evidence of luminal haziness, parietal irregularities or mild atheromasias (MCA, ie, a 30%-50% stenosis in one or more coronary arteries as shown by CA) can be clues to an underlying plaque disruption in MINOCA (Fig 2).[10] However, the identification and classification of plaque disruption in vivo can be a challenging task when solely relying on CA.[10] In recent years, the increasing use of intracoronary imaging has revealed that plaque disruption can be present in normal-appearing coronary segments, yet it is never observed in patients with angiographically normal coronary arteries.[13-15]

A seminal intravascular ultrasound (IVUS) study showed that atherosclerotic plaque disruption – most commonly PR – is identifiable in 38% of women with MINOCA.[14] Another smaller study investigating optical coherence tomography (OCT) found a similar burden of plaque disruption

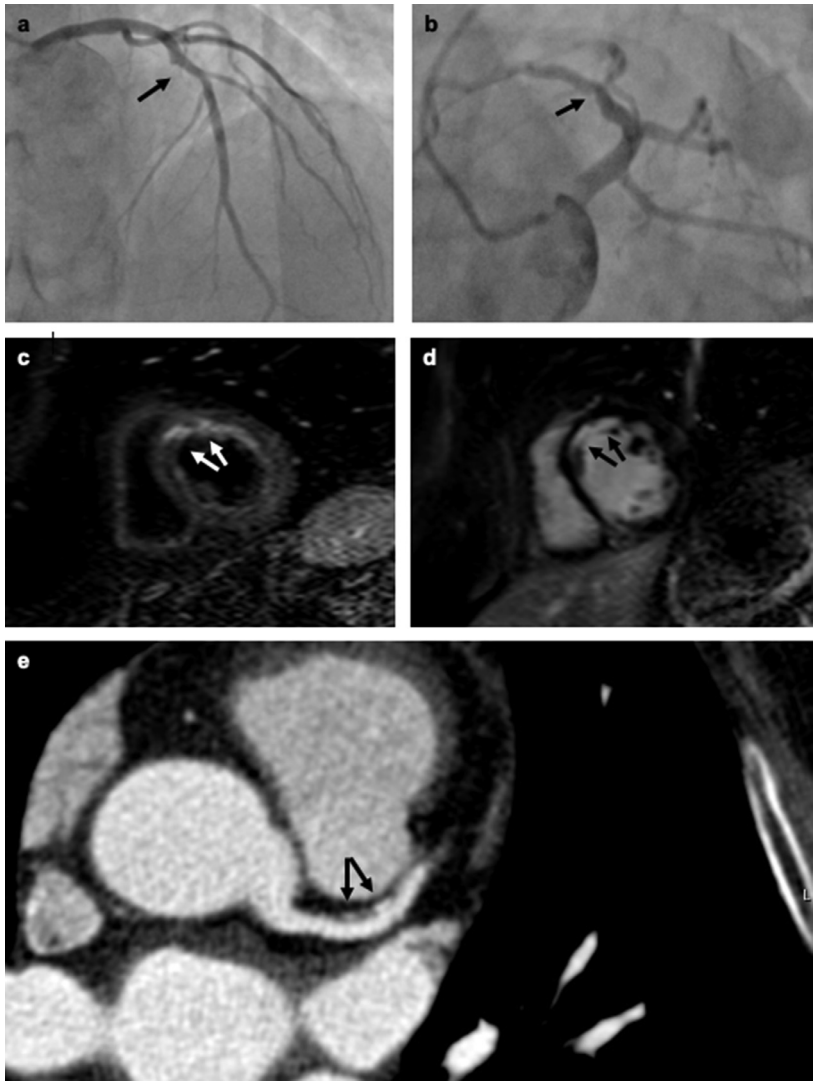

FIG 2. Multimodality imaging approach in a case of type 1 MINOCA. A 54-year-old male presented with chest pain, positive troponin assay and ST-segment elevation in anterior-septal leads. Panels a and b: coronary angiography revealing a non-obstructive (≤50%) lesion (arrows) of the proximal left anterior descending (LAD) coronary artery. Panels c and d: contrast enhanced cardiac magnetic resonance imaging (CE-CMR), short-axis views. Panel c: T2 weighed short-tau inversion recovery (T2-STIR) image, showing edema in the basal septal and anterior segments of the left ventricle (arrows). Panel d: phase sensitive inversion recovery (PSIR) image, revealing subendocardial scar in the same segments (arrows). Panel e: coronary computed tomography scan confirmed a non-obstructive and mixed atherosclerotic lesion of the proximal LAD (arrows). The patient was treated with aspirin, clopidogrel, atorvastatin, metoprolol, and zofenopril.

(35%) and, interestingly, a 11% prevalence of PE.[15] Although no study to date directly compared IVUS to OCT in MINOCA, this latter technique might be preferable, by allowing identification of subtler irregularities of the coronary artery surface and showing luminal thrombosis, thus enabling better identification of PE.[10,15] On the basis of the available evidence, we advocate a wider use of 3-vessel OCT in MINOCA patients with MCA, when other causes for the clinical presentation are excluded (Fig 3).

Type 2 MINOCA

Type 2 MINOCA is defined by the presence of MI secondary to myocardial oxygen supply/ demand imbalance in the absence of acute atherothrombosis and coronary stenoses $\geq$50%.[6,16] Identification of the ischemic mechanism is of paramount importance in order to distinguish type 2 MINOCA from myocardial injury.[6] Type 2 MINOCA can be produced by both coronary and noncoronary causes,[6,16] as listed below:

1) Coronary causes: coronary artery spasm (CAS), coronary microvascular disfunction (CMD), spontaneous coronary artery dissection (SCAD), and/or intramural hematoma, coronary thrombosis, or embolism;
2) Noncoronary causes: severe tachy- or brady-arrhythmias, severe hypertension or hypotension, marked left ventricular hypertrophy, severe anemia; prolonged hypotension/shock, severe hypoxia, or respiratory failure.

Coronary artery spasm. CAS is identifiable as the causative mechanism of MINOCA in more than 40% of cases,[17] and East Asians seem to have a stronger predisposition for CAS.[18,19] CAS is defined as a marked (>90%) focal or diffuse reduction in the calibre of an epicardial coronary artery, and it can either be spontaneous or provoked by triggers, such as cocaine or 5-fluorouracil.[18,19] CAS can be asymptomatic and incidentally discovered during CA[18,19]; however, when associated with chest pain (typically at rest and in the early morning hours, usually triggered by hyperventilation or alcohol consumption) and ischemic ECG changes, the term vasospastic angina (VSA) is applied.[19] When severe and prolonged, CAS can lead to a MI.[17-19]

Interestingly, animal models and early human series have shown that CAS usually insists over coronary atherosclerotic lesions[19]: nonetheless, coronary obstruction is not prerequisite for spasm, and CAS can occur in smooth arteries.[20]

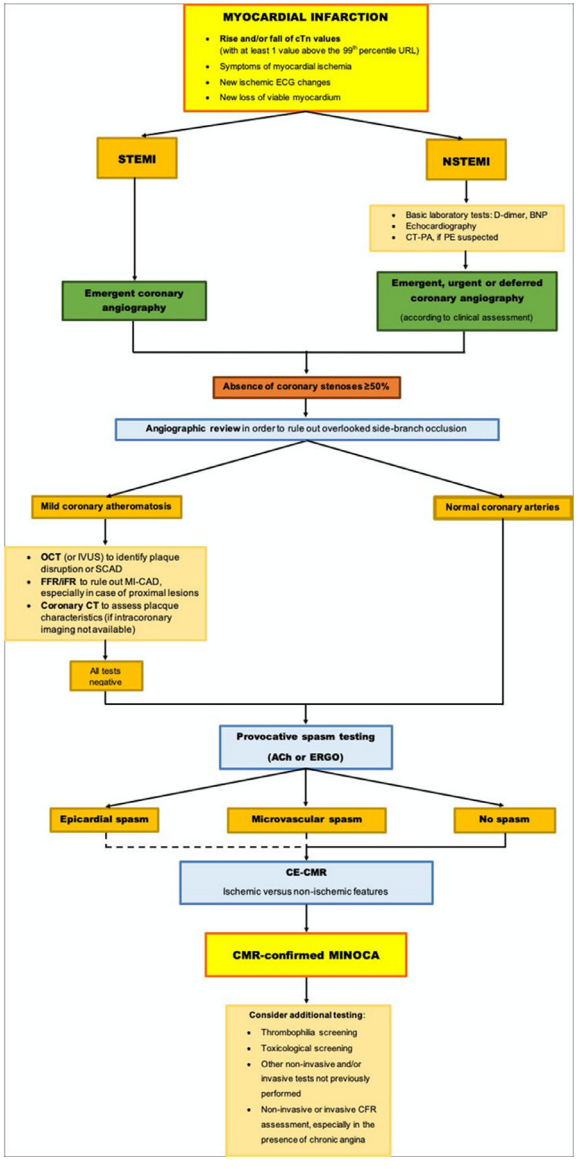

FIG 3. Comprehensive stepwise diagnostic approach to myocardial infarction without obstructive coronary artery disease. Abbreviations: ACh, acetylcholine; BNP, brain natriuretic peptide; CE-CMR: contrast-enhanced cardiac magnetic resonance; CFR, coronary flow reserve; CMR, cardiac magnetic resonance; cTn, cardiac troponin; CT, computed tomography; CT-PA, computed tomographic pulmonary angiography; ERGO, ergonovine; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction without obstructive coronary artery disease; NSTEMI, non ST-segment elevation myocardial infarction; OCT, optical coherence tomography; PE, pulmonary embolism; STEMI, ST-segment elevation myocardial infarction; URL, upper reference limit.

Table 2. Commonly used provocative spasm testing protocols

Acetylcholine	Ergonovine
1. Place a temporary PM in the RV 2. Basal angiography of both LCA and RCA, taking care to optimize the projection 3. Sequentially inject 20, 50, and 100 μg boluses of ACh in 37˚C NaCl 0.9% solution (adjusting the concentration in order to obtain 5 mL volume for each bolus of ACh) into the LCA over a period of 20 seconds at 5-minute intervals. Perform angiography 1 minute after the start of each injection or earlier in case of ischemic symptoms and/or ECG changes 4. Sequentially inject 20 or 50 μg of ACh (same dilution as for the LCA) into the RCA over a period of 20 seconds, and perform angiography with the same timing as for the LCA 5. Inject a nitrate and perform control-angiography at the time of maximal dilation for both LCA and RCA	1. Basal angiography of both LCA and RCA, taking care to optimize the projection 2. Inject 20-60 μg of ERGO in NaCl 0.9% solution into the LCA over a period of 2-5 minutes. Perform angiography 1-2 minutes after the end of injection or earlier in case of ischemic symptoms and/or ECG changes 3. After 5 minutes, inject ERGO (same amount and dilution as for the LCA) into the RCA over a period of 2-5 minutes. Perform angiography with the same timing as for the LCA 4. Inject a nitrate and perform control-angiography at the time of maximal dilation for both LCA and RCA

Abbreviations: ACh, acetylcholine; ECG, electrocardiography; ERGO, ergonovine; LCA, left coronary artery; PM, pace-maker; RCA, right coronary artery; RV, right ventricle.
Adapted from JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic *Angina) (JCS 2013). Circ J 2014; 78(11):2779-801.*

Although occasionally spontaneous episodes of CAS can be identified during CA, CAS is more commonly elicited by provocative tests.[18,19] Nowadays, the preferred methods involve intracoronary acetylcholine or ergonovine injection at increasing doses, evaluating patient's clinical, electrocardiographic and angiographic responses (Table 2).[18,19] The diagnostic accuracy of provocative testing has not yet been formally assessed in MINOCA; however, sensitivity and specificity in patients with VSA (most of whom had nonobstructed coronary arteries) were 90% and 99%, respectively.[20]

Despite rarely performed out of fear of complications, provocative tests are safe, with a reported rate of major complications (mainly arrhythmias) of 1% when performed on stable patients.[18-21] Furthermore, most adverse events can be successfully managed by administering intracoronary nitrates.[18-21] To date, the only pilot study in which provocative tests were performed in MINOCA patients early-on after admission included 80 patients.[17] Interestingly, provocative testing enabled the identification of epicardial CAS and microvascular spasm in 30% and 16% of patients, respectively.[17] Patients with positive test results had greater risk of long-

term cardiovascular events or death, and no adverse events were reported.[17] Therefore, provocative testing could have an important diagnostic and prognostic yield in MINOCA, while being overall safe.[17] Accordingly, the most recent European guidelines for the management of patients with ACS suggested that provocative testing for CAS might be considered in selected patients with a recent MI and suspected VSA.[7,22]

Coronary microvascular dysfunction (CMD). One major limitation of CA is that it only allows direct inspection of epicardial coronary arteries. However, prearterioles, arterioles, and capillaries, collectively designed "coronary microcirculation,"[23] play pivotal roles in the regulation of coronary flow and in a plethora of cardiac diseases, either as primary determinants (type 1 CMD) or as secondarily affected elements in cardiomyopathies (type 2 CMD), obstructive CAD (type 3 CMD) or iatrogenic (reperfusion-related) injury (type 4 CMD).[23] CMD can be a potential mechanism of MINOCA, either *per se*, as in the case of prolonged and intense microvascular spasm,[10,24] or as a concurrent determinant of ischemic damage, when the coronary microcirculation gets impinged by atherothrombotic debris produced by plaque disruption in a proximal coronary segment.[10,23,24]

The clinical definitions of CMD include either a pathological (ie, <2-2.5) reduction in coronary flow reserve (CFR), or coronary microvascular spasm, or the coronary slow-flow phenomenon.[10,25] Historically, CFR could only be measured by invasive investigations (ie, thermodilution catheter or Doppler flow wires) in selected referral centres.[23,25] However, more recently, noninvasive methods (transthoracic Doppler echocardiography, positron emission tomography, or contrast-enhanced cardiac magnetic resonance, CE-CMR) were found to be reliable, while being more widely available.[23,25] Coronary microvascular spasm can be identified by the same intracoronary provocative tests discussed above, when chest pain and ischemic ECG changes are induced but epicardial CAS is not observed.[23-25] The coronary slow-flow phenomenon is characterized by a prolongation of the time needed to fill an epicardial coronary artery with contrast dye (≥3 beats), indicating heightened coronary microvascular resistance, and can be semiquantitatively assessed with the thrombolysis in myocardial infarction frame count, which is a simple and immediately available method.[10,25]

The clinical usefulness of the various tests for CMD in the setting of MINOCA is not clearly established.[10] However, at present, the thrombolysis in myocardial infarction frame count might be considered a low-cost first-level assessment in order to rapidly evaluate the coronary

microcirculation, while provocative spasm tests, by simultaneously exploring the function of both larger and smaller coronary vessels, could be considered promising second-level investigations. Measurements of CFR seem most fruitful for patients with suspected microvascular angina, a chronic coronary syndrome due to CMD which is commonly observed in women and is characterized by chronic effort or cold-induced chest pain.[25]

Spontaneous coronary artery dissection. SCAD is another important yet overlooked cause of type 2 MINOCA.[10,26,27] SCAD is defined as an intramural hematoma occurring in the *tunica media*, not associated with trauma, atherosclerosis, or medical interventions.[26,27] When SCAD determines a critical limitation of coronary blood flow, MI ensues; nonetheless, angiographic evidence of obstruction in a coronary artery is not prerequisite for SCAD diagnosis, and SCAD can be inapparent by CA, especially when it produces a diffuse and gradual narrowing in a coronary artery branch.[10,26,27] Moreover, overlooking of SCAD could be provoked by contrast medium flush, which can compress the false lumen by increasing pressure in the true lumen at the time of CA, thus challenging the diagnosis of SCAD by CA.[26,27] Therefore, although it is difficult to precisely measure, an underestimated proportion of MINOCAs may be due to SCAD, which should be primarily suspected in women of reproductive age, especially during pregnancy.[10,26-28] Hopefully, the increasing use of intracoronary imaging modalities will improve diagnostic capabilities.[29,30] Even in this context, OCT seems preferable over IVUS, by allowing clearer visualization of lumen-intimal interface and intramural hematoma.[29,30]

Two different mechanisms have been proposed to explain SCAD. According to the first one, intimal rupture provokes extravasation of blood into the medial layer, forming a false lumen that can potentially compress the true coronary artery lumen.[26,27] The second hypothesis postulates that hemorrhage in the *tunica media* is the initiating event and intimal rupture may be a secondary phenomenon related to the increased pressure in the false lumen.[26,27]

The multifactorial pathophysiology of SCAD seems dependent on both a predisposing substrate weakening the coronary artery wall (such as fibromuscular dysplasia, hormonal factors in pregnancy, inflammatory conditions or genetic syndromes such as Marfan, vascular Ehler-Danlos or Loeys-Dietz) and a triggering event, most commonly extreme physical or emotional stress.[26-30]

Coronary thrombosis and embolism. Coronary thrombosis can occur in intact coronary vessels as a result of a genetic or acquired thrombophilia

and produce a nonobstructed angiographic picture in case of spontaneous lysis of the thrombus or distal embolization.[6,8,11] With regard to genetic thrombophilias, a systematic review found that as many as 14% of MINOCA patients had a hereditary prothrombotic state, most commonly the Leiden factor V mutation.[8] Reported risk of MINOCA among subjects with this genetic variant ranges from 1.3% to 3.7%.[31,32]

Coronary embolism is another determinant of MINOCA when it involves the coronary microcirculation.[5,10] It can be produced by atrial fibrillation, distal embolization of coronary thrombi, paradoxical embolism or other conditions in which nonthrombotic material gets dislodged in the systemic circulation, such as endocarditis or cardiac neoplasia.[5,6,10] The clinical presentation is highly variable, and can be dominated by symptoms of systemic (ie, cerebral) embolism. If the clinical picture is unclear, it is reasonable to exclude pulmonary embolism, which is a well-known noncoronary cause of cardiac troponin rise.[5,6,10]

The indications and utility of testing for genetic or acquired thrombophilias are currently undefined, and these tests should preferably be performed in consultation with a haematologist.[8,10]

Noncoronary causes. Supply-demand mismatch due to noncoronary mechanisms is the last major cause of type 2 MINOCA, and it is most commonly encountered among critically ill and old patients.[6,10,16] Severe anemia, respiratory failure, hypotension/shock, marked hypertension, and sustained tachy- or brady-arrhythmias may be important elements precipitating the ischemic imbalance, by simultaneously reducing coronary perfusion and increasing myocardial oxygen requirements.[6,10,16] In these patients, MCA may act as an important modulating factor, by lowering the ischemic threshold.

Type 3 MINOCA

Type 3 MI is defined as the occurrence of sudden cardiac death (SCD) in a patient with symptoms of myocardial ischemia, ischemic ECG changes and/or ventricular fibrillation, just before biomarkers can be measured, or before increases in cardiac biomarkers can be detected, or when MI is identified by autopsy examination, in the absence of autopsy-proven coronary stenoses $\geq$50%.[6] There is a paucity of reports regarding patients who suffered a SCD and had a pathological diagnosis of MINOCA, but the misuse of drugs and illicit substances seems implicated in the majority of cases.[33]

In a recent retrospective cohort of patients suffering of sudden death and which underwent cardiac pathological examination the prevalence of MINOCA as the cause of sudden death has been detected in the region of 0.5%-1%.[34] Among this subgroup of decedents the same authors reported illicit drug use in 1 of 3 patients. Moreover, in the same study, coronary thrombosis was found exclusively found among patients with nonobstructive coronary atherosclerosis (in 7 out of 10), thus in remaining patients with completely normal coronary arteries it is possible to hypothesised a causative role for coronary spasm in the etiology of MI and subsequent sudden death.[34]

Comprehensive stepwise diagnostic approach

Clinical judgment should guide clinicians in the selection of the most appropriate sequence of tests for the diagnosis of MINOCA, as depicted in Figure 3.[10] Five key points deserve a special mention.

Left ventricular angiography (LVA) has been advocated as a first-level test in order to recognize an epicardial or microvascular pattern in patients with MINOCA and identify Takotsubo syndrome.[35] However, most of the information derived from LVA can be also obtained with echocardiography, and it is our opinion that LVA should be limited to patients without prior echocardiographic assessment or with uninterpretable echocardiography and without severe kidney disease. in patients with MCA, OCT (or, alternatively, IVUS) should be considered in order to rule-out plaque disruption or SCAD, and should be performed early on, ideally during the index CA, in order to inform the therapeutic approach.[10,14,15] If intracoronary imaging is not available, important information on coronary plaques characteristics could be obtained by coronary computed tomography scan.[36]

1) Although the role of fractional/indexed flow reserve (FFR/iFR) has not been systematically analyzed in MINOCA,[10] recent evidence suggests that a more liberal use of FFR in patients with MCA would allow reclassification of a high proportion of coronary lesions as functionally significant, supporting a diagnosis of MI-CAD.[17] Currently, there is no solid evidence to inform a dichotomous choice between anatomical and functional intracoronary tests; however, in light of the available data, the former seem preferable when resources are limited;
2) provocative spasm testing with acetylcholine or ergonovine is another cornerstone in the approach to MINOCA, given its safety

and high diagnostic yield[10,17,37] by allowing simultaneous assessment of epicardial as well as intramyocardial coronary vessels.[17,24] The ideal collocation of provocative testing in a diagnostic flowchart for MINOCA is currently highly debated and might reasonably be adapted to the global clinical picture (Fig 2);

3) confirming ischemia is a necessary step over a correct MI diagnosis.[6] In addition to the clinical and ECG presentation, CE-CMR is an important tool in uncertain cases.[38,39] In fact, CE-CMR can detect even subtle signs of a MI (CMR-confirmed MINOCA), or show suggestive evidence of myocarditis or other cardiomyopathies, with high diagnostic yield.[10,38,39] Furthermore, CE-CMR helps with prognostication: in a recent series, patients with CMR-proved cardiomyopathy had markedly worse outcomes than patients with CMR-confirmed MINOCA.[39] However, CE-CMR is not prerequisite to a diagnosis of MINOCA, which can be formulated on the basis of clinical and angiographic data (not CMR-confirmed MINOCA) and, accordingly, CE-CMR can be performed later on during hospitalization.[5,10] Of note, current European guidelines state that CMR is recommended in all MINOCA patients without an obvious underlying cause (Class I; Level of Evidence B).[7]

Prognosis

Unlike the common perception, there is increasing evidence that the prognosis of MINOCA is of concern.[8] Data from large numbers of patients from different studies revealed an all-cause in-hospital and 12-month mortality of 0.9% and 4.7%, respectively.[8] These figures indicate a considerable risk, similar to that associated with MI-CAD according to some recent reports.[40]

Several clinical and angiographic features have been reported as independent predictors of adverse outcomes: C-reactive protein,[9] MCA involving 3-vessels and/or the left main coronary artery,[9] atypical symptoms,[41] ST-elevation,[39,41] Killip class IV at admission,[41] diabetes mellitus,[41] and the elicitation of coronary spasm by provocative testing.[17]

It is, however, worth noticing that many studies are biased by the use of administrative data and inappropriate labeling of other conditions (ie, cardiomyopathies, myocarditis, takotsubo syndrome, and pulmonary embolism) as MINOCA. Therefore, currently available data on prognosis should be cautiously weighed.[8,40,41]

Therapy

As MINOCA is not a single entity but a heterogeneous group of different clinical conditions, the therapeutic approach should be personalized, by addressing the specific underlying mechanism(s) (Table 3).

Antithrombotic therapy

For patients with type 1 MINOCA, antithrombotic agents are the cornerstone of treatment, by translating evidence derived from MI-CAD trials, in which antiplatelet agents were administered even in absence of CA.[42,43] In these studies, the addition of clopidogrel to low-dose aspirin consistently proved beneficial in terms of hard clinical endpoints.[41,42] In a recent observational study, however, dual antiplatelet therapy had neutral effects on outcomes of MINOCA patients,[11] although the population studied was highly heterogeneous and probably included many cases of myocarditis and/or Takotsubo syndrome.[44] There are no specific studies addressing the use of anticoagulants in MINOCA.

Beta-blockers

The use of beta-blockers has been reported to reduce recurrences among patients affected by SCAD[45] and to be associated with a not significant trend toward benefit in the aforementioned observational MINOCA study.[11] Caution should be used in cases of proven CAS, although selective beta-blockers could be considered when there is a fixed component of coronary obstruction in addition to dynamic spasm.[19]

Statins

Statins were shown to have long-term beneficial effects for the secondary prevention of cardiovascular events in patients with MINOCA,[11] and their use should be strongly considered in any case in which there is evidence of atherosclerosis, even if subtle (ie, MCA).

Agents modulating the renin-angiotensin-aldosterone system

Agents modulating the renin-angiotensin-aldosterone system are well known to have significant cardioprotective effects.[46] In the aforementioned observational study,[11] angiotensin converting enzyme-inhibitors and angiotensin-receptor blockers proved effective in improving prognosis of patients with MINOCA. There are no specific data on

Table 3. Management approach to type 1 and type 2 MINOCA

MINOCA	General investigations		Specific investigations	Specific therapeutic measures
	• Basic laboratory tests including cTn • ECG • TTE • CA with careful angiographic review • CE-CMR • Consider FFR	Type 1	• OCT (IVUS)	• Aspirin, Clopidogrel/Ticagrelor, Statin, ACE-inh/ARB, BB
		Type 2	Epicardial CAS • Provocative spasm testing • Toxicological screening	• Avoidance of triggers and lifestyle changes • CCBs, nitrates, Nicorandil, Fasudil, consider statin and ACE-inh/ARB
			Microvascular Dysfunction • Provocative spasm testing • CFR measurement	• Microvascular spasm: avoidance of triggers and lifestyle changes; CCBs, nitrates. • Reduced CFR: lifestyle changes, BB, statin, ACE-inh/ARB, ranolazine
			SCAD • OCT (IVUS)	• Aspirin and BB • Consider Clopidogrel
			Coronary thrombosis or embolism • OCT (IVUS) • Thrombophilia Screening • TEE	• Aspirin, P2Y12 inhibitor, Anticoagulant, PFO occlusion, endocarditis treatment
			Non-coronary causes • Vital signs and clinical assessment • Blood gas analysis	• Treatment according to the identified cause (anti-hypertensive drugs, BB, fluids, transfusions, oxygen)

Abbreviations: ACE-inh, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CA, coronary angiography; CCB, calcium channel blocker; CE-CMR, contrast-enhanced cardiac magnetic resonance; CFR, coronary flow reserve; cTn, cardiac troponin; ECG, electrocardiogram; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MINOCA, myocardial infarction without obstructive coronary artery disease; OCT, optical coherence tomography; PFO, patent foramen ovale; SCAD, spontaneous coronary artery dissection; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

mineralocorticoid-receptor antagonists, which should be reserved to patients with MINOCA and moderately/severely reduced left ventricular ejection fraction.

Calcium channel blockers and other vasodilators

When epicardial CAS is identified, calcium channel blockers (CCBs) are the first-line option, not only because they are efficacious in the control of symptoms, but also because they are related to favorable long-term prognosis.[17,19] Among CCBs, both dihydropyridine and nondihydropyridine agents have been shown to be effective.[19] Nitrates are usually prescribed as an adjunct to CCBs for long-term control of symptoms, although their prognostic role is uncertain.[47] Other vasodilating agents with proven effectiveness for CAS include nicorandil, cilostazol, and fasudil.[19]

General and additional measures

It seems reasonable that cardiovascular risk factors are aggressively addressed after a MINOCA.[11,46] Furthermore, potential triggers for spasm, including smoking, illicit drugs, serotoninergic or ergot compounds, chemotherapeutic agents such as 5-fluorouracil, capecitabine, and sorafenib should be avoided.[19]

In case of CMD, there are limited data on the use of CCBs, beta-blockers, statins, enalapril, ranolazine, dipyridamole, which might all improve coronary microvascular flow and alleviate anginal symptoms.[23]

When clinical presentation is consistent with a supply-demand mismatch, inciting factors should be promptly identified and corrected. Antithrombotic agents have little or no role in this subset.[16] Recently released European guidelines state that "patients with a final diagnosis of MINOCA of unknown cause may be treated according to secondary prevention guidelines for atherosclerotic disease" (Class IIb; Level of Evidence C).[7] However, high-quality evidence from prospective, randomized, controlled trials is lacking.

Knowledge gaps and future perspectives

Many issues still need to be addressed in depth with regard to MINOCA. First, the arbitrary angiographic 50% cut-off could be arguable, as a 40% narrowing in the left main coronary artery may not have the same functional significance as a similar degree of stenosis in a distal vessel and, therefore, FFR should be more widely performed in these

patients.[10] Second, a priori exclusion of confounding diseases such as myocarditis and Takotsubo syndrome should be required in studies investigating MINOCA, given the different mechanisms underlying these conditions.[7,44] Third, the role of the various pharmacological therapies for the secondary prevention of cardiovascular events remains unclear.[7]

Conclusions

Interest around MINOCA has greatly grown in the last few years. Advanced diagnostic tools, such as intracoronary anatomical, functional or provocative testing and CE-CMR, should be employed more liberally once obstructive CAD is ruled out by CA, ideally following a rational comprehensive diagnostic workup. These tests, although expensive and not universally available, can allow the identification of specific pathophysiological mechanisms, which can be targeted by tailored treatments. Further research aiming at unravelling novel mechanistic insights and developing targeted therapeutic measures is warranted in order to achieve the goal of improving patients' prognosis.

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Conflict of interest

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