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Invited Review Article

Myocardical Infarction with Non-Obstructive Coronary Arteries (MINOCA): pathogenesis, diagnosis and treatment

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ABSTRACT

The term MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries) refers to myocardial infarction cases where coronary arteries exhibit less than 50 % stenosis. MINOCA encompasses a diverse range of pathologies with varying etiologies. Diagnosis involves meeting acute myocardial infarction criteria and excluding other causes (myocarditis, takotsubo syndrome). Clinical features often resemble those of traditional myocardial infarction, but MINOCA patients tend to be younger and more frequently female. Etiological investigations include coronary angiography, intracoronary imaging, and vasomotor function tests. Causes include plaque rupture, coronary dissection, vasospasm, microvascular dysfunction, thromboembolism. Prognosis varies, with some subsets at higher risk. Management involves a tailored approach addressing underlying causes, with emphasis on cardioprotective therapy, risk factor modification, and lifestyle interventions. Further research is needed to refine diagnostic strategies and optimize therapeutic approaches in MINOCA patients.

Introduction

The term MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries) refers to any condition responsible for myocardial ischemic necrosis associated with angiographic documentation of the absence of hemodynamically significant coronary lesions (stenosis < 50 %)[1].

From this definition, it can be inferred that the term MINOCA refers to the final event, namely myocardial infarction, rather than the underlying pathology, and that such terminology refers to a heterogeneous group of pathologies, sharing the aforementioned characteristics. The term MINOCA should constitute an operational diagnosis in order to identify the specific etiology in individual patients.[1]

To diagnose MINOCA, it is essential that the criteria for acute myocardial infarction (AMI) be satisfied, as defined by the joint consensus document of the Fourth Universal Definition, drawn up by the leading international cardiology societies,[2] which includes the MINOCA theme among its new sections (Fig. 1).

In recent studies, events classifiable as MINOCA represent approximately 6–8 % of AMI diagnoses.[4–6] However, the documented prevalence in the literature varies considerably, reaching peaks of 25 %,[7] mainly due to the lack of a unified protocol for MINOCA diagnosis, leaving open the possibility that other inadequately excluded pathologies may have influenced individual cases. In fact,

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even recent and extensive case studies, such as the Swedish one described by Lindahl et al,[4] including 9136 patients, encompass and describe the prognosis of patients with troponin progression from AMI and angiographically intact or < 50 % lesioned coronary arteries, without defining the etiological causes and without being able to exclude other diagnoses such as acute myocarditis or Takotsubo syndrome as cases of MINOCA. Similarly, the main meta-analysis on the subject[5] includes 18 % Takotsubo syndrome and 33 % acute myocarditis estimated from MINOCA studies that underwent cardiac magnetic resonance imaging (CMR), a diagnostic method mostly able to differentiate between coronary and non-coronary causes.[7]

Comparing the population of subjects with myocardial infarction due to obstructive coronary artery disease (MI-CAD), MINOCA patients are generally younger, with a mean age at presentation of around 55 years and only a slight male preponderance.[8,9] The female sex is therefore proportionally more represented compared to the MI-CAD counterpart, with values around 40 %.[5] The profile of cardiovascular risk factors in MINOCA patients does not substantially differ from the MI-CAD population, except for a lower prevalence of hyperlipidemia.[5] At the time of diagnosis, approximately two-thirds of MINOCA present an electrocardiographic pattern classifiable as AMI without ST-segment elevation (NSTEMI), while in the remaining third, the presentation is that of myocardial infarction with ST-segment elevation (STEMI).[5]

Recent studies on the relationship between MINOCA and personality traits have shown that there is no significant difference between MINOCA patients and MI-CAD patients.[10] Anxiety and depression are frequent in MINOCA patients compared to those with MI-CAD[11,12] and are directly correlated with poor prognosis.[13] The seasonal variability of MINOCA and MI-CAD is different, with the incidence of MINOCA slightly increasing in summer and autumn.[14]

Pathogenesis and search for etiological cause

As emphasized in the ESC position paper,[3] the term MINOCA should be understood as an operational diagnosis, meaning it serves as a starting point for identifying the underlying etiological cause. Patient history (age, sex, cardiovascular risk factors, family history, comorbidities) and clinical presentation (onset mode of pain, preceding symptoms) play a critical role in suspecting the cause responsible for MINOCA and guide the cardiologist in requesting further diagnostic investigations[1] (Table 1). In fact, angiography alone in most cases does not lead to an etiological diagnosis. The use of intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), increases the ability to identify plaque rupture and/or erosion, coronary dissection, or endoluminal thrombosis.[1] However, it is important to note that even with this instrumentation, it is not always possible to reach an etiological diagnosis with a certain degree of certainty.

Two main groups of causes responsible for MINOCA can be identified:

1. Epicardial Causes:
   - Plaque rupture and/or erosion of coronary plaque
   - Coronary dissection
   - Epicardial vasospasm
2. Microvascular Causes:
   - Microvascular vasospasm
   - Thromboembolism
   - Non-ischemic causes such as myocarditis and Takotsubo syndrome.

Regarding Takotsubo syndrome, some authors consider it as a condition secondary to a coronary cause due to microcirculation ischemia and therefore include it among MINOCA, while others consider it a non-involvement of epicardial coronaries and thus include it among the differential diagnoses to be excluded.[1] The ESC position paper includes Takotsubo syndrome among the

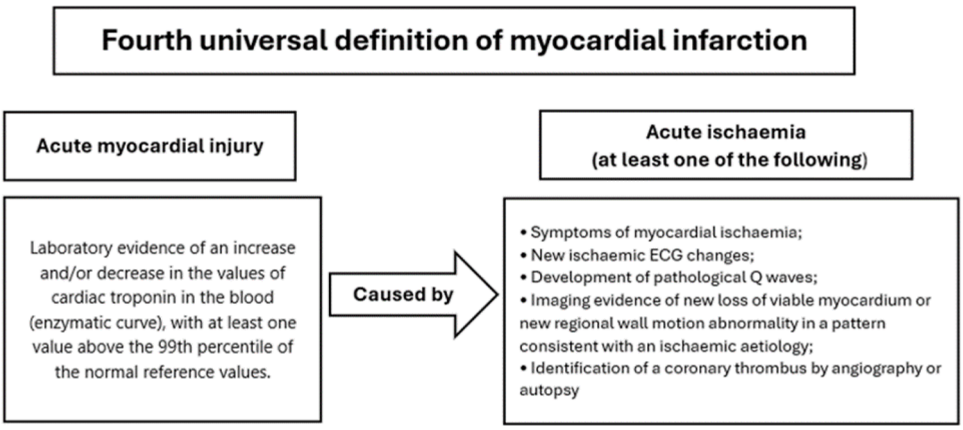

Fig. 1. Diagnostic alghorithm for MINOCA.

non-coronary causes of troponin elevation,[3] and in some cases, such as that of Ciliberti et al,[15] it is excluded.

The difference between the two groups is determined by the presence of ventricular wall motion abnormalities, identifiable by echocardiography or ventriculography. In cases of involvement of epicardial vessels, this manifests as territorial abnormalities consistent with the involved coronary artery, while in cases of microcirculatory dysfunction, it does not match the epicardial perfusion.

The main causes identified as responsible for MINOCA are described below.

Plaque Rupture and/or Erosion.

Rupture of an atherosclerotic plaque is one of the most common causes of MINOCA, as demonstrated by studies using intracoronary imaging, which have shown a prevalence of approximately 40 %.[16,17] Initially, there is plaque rupture, endothelial disruption causing thrombosis, and partial or total occlusion of the coronary lumen, but the degree of stenosis will be <50 %.[18] The thrombotic process may be accompanied by phenomena of more peripheral thromboembolism and/or vasospasm and is followed, according to the most accredited theory, by thrombolysis or spontaneous lysis,[19] which is why complete vascular occlusion is not found at the time of angiographic study. It has been shown that sometimes the rupture of a plaque with modest lipid content, if occurring in a context where multiple prothrombotic factors overlap, can result in complete intracoronary occlusion.[20,21] The use of intravascular imaging techniques such as IVUS and OCT is crucial in assessing possible plaque erosion.[1]

Coronary Dissection.

Spontaneous coronary artery dissections (SCAD) are a well-known cause of SCA and are due to the acute development, more frequently through the fissuring of the endothelium of the intima, of a false lumen within the coronary wall, which creates obstruction to flow due to external compression of the true lumen.[22] The overall incidence is not known due to a likely underestimation of the phenomenon, but there is a prevalence in young and middle-aged women, as demonstrated in a Canadian study where SCAD represented the mechanism responsible for 24 % of SCA in women aged <50 years.[23] Pregnancy and the postpartum period,[24] as well as the presence of fibromuscular dysplasia,[25] characterized by stenoses, dissections, and aneurysms involving medium-caliber arteries, have been associated with the onset of SCAD and are historical findings to be considered in formulating the diagnostic suspicion. Despite some typical angiographic patterns being codified, suspicion of coronary dissection may not be apparent during angiographic evaluation.[26] Again, the use of intracoronary imaging techniques such as IVUS and OCT is crucial.[1]

Coronary Vasospasm.

Coronary vasospasm represents an overactive response of the smooth muscle component of the coronary wall and endogenous vasoconstrictor substances, configuring the picture of vasospastic angina, or exogenous (drugs such as cocaine or amphetamines)[27,28] and is one of the main causes of vasospasm of the epicardial vessels in MINOCA despite the pathology can also affect the microcirculation. The prevalence of vasospastic angina in patients with MINOCA varies greatly, from 3 % to 95 %, depending on the adopted definition, ethnicity, and the use or not of provocative tests. A recent study[29] published by the Coronary Vasomotion Disorders International Study Group (COVADIS) aimed to standardize diagnostic criteria for vasospastic angina. The main warning signs that lead to suspicion of this diagnosis concern the presence of anginal episodes occurring at rest, especially at night or early in the morning, which regress after taking nitrates or calcium antagonists, and which can be exacerbated by hyperventilation and smoking. The diagnosis is definitive if during an episode with the aforementioned characteristics, typical electrocardiographic changes (both ST-segment elevation and depression) are documented, in the absence of other causes that can justify the symptoms. Often, this does not occur in clinical practice, so it is necessary to perform provocative tests during angiography using acetylcholine or ergonovine. The test is considered positive if there is:

- Appearance of anginal symptoms.
- Appearance of electrocardiographic changes.
- Appearance of coronary spasm in one or more epicardial coronaries with luminal narrowing >90 % compared to the reference caliber.[30]

In the absence of the latter characteristic but with the presence of the previous two, it is possible to hypothesize a localization of the spasm in the microcirculatory district.[31] A study conducted by Montone et al[32] demonstrated that in a population of MINOCA, 46 % of patients tested positive for coronary vasospasm, with about two-thirds in the epicardial district and one-third in the microcirculation.

Microvascular Vasospasm.

Transient transmural myocardial ischemia can occur during a spontaneous or induced angina attack, during which the ECG shows ST segment depression, but the epicardial coronary arteries are absolutely intact.[33,34] If the provocative test with acetylcholine is positive, with the respective electrocardiographic picture, but there is no epicardial spasm, then a diagnosis of microvascular angina can be made.[35,36] Previous studies[37] have highlighted that approximately 16 % of patients with MINOCA present microcirculatory vasospasm.

Coronary Thromboembolism.

Coronary thromboembolism may represent a mechanism overlapping with atherosclerotic plaque rupture or vasospasm, but it can also be the sole mechanism responsible for MINOCA. It is a rare cause of ACS, with an observed incidence of 3 %.[38] Excluding iatrogenic forms, coronary thromboembolic episodes can be distinguished into direct and paradoxical forms.[39] Direct forms are characterized by the localization of the embolic source in the left sections of the heart: atrium, ventricle, pulmonary veins, endocarditic processes involving the mitral and aortic valves, rarely cardiac tumors, and even primary origin in the coronary district, for example, from embolization of more proximal coronary aneurysms.[40] They represent the most frequent forms, especially those associated with atrial fibrillation, responsible for approximately 73 % of all episodes.[38] Paradoxical forms presuppose the formation of the thrombus in the venous circulation and its subsequent passage into the coronary district through the presence of an intracardiac communication (e.

g., patent foramen ovale or atrial septal defect) or extracardiac communication (e.g., pulmonary arteriovenous malformation). Criteria, divided into major and minor, have been proposed for the definitive or probable diagnosis of coronary thromboembolism.[41] In the diagnostic workup, all conditions potentially associated with the development of thromboembolism must be excluded: it is necessary to search for the presence of atrial fibrillation and endocarditic processes, which constitute the first and second most frequent causes of embolic forms. The presence of hereditary thrombophilic states (factor V Leiden, protein C and S deficiency), both acquired (antiphospholipid antibody syndrome and myeloproliferative syndromes), plays a role not yet entirely clarified in the context of coronary thromboembolic phenomena.[1] A systematic review[6] highlighted the prevalence of 14 % of hereditary thrombophilic disorders in patients with MINOCA.

Takotsubo Syndrome.

Although it can be classified as a form of ACS, there are still doubts about the pathophysiological mechanisms responsible for myocardial damage. It is known that hyperactivation of the sympathetic nervous system plays a central role, but how this can cause myocardial damage is not yet fully understood: the most plausible hypotheses involve a direct toxic effect of toxins on cardiomyocytes,[41] but also an effect mediated by vasoconstriction of epicardial coronary arteries and, especially, of the microcirculation, whose dysfunction plays a central role.[42] It is precisely these two pathophysiological hypotheses that allow classifying Takotsubo syndrome within the MINOCA group.[43] The incidence is about 1–3 % of all STEMIs, and approximately 90 % of affected patients are postmenopausal women.[44,45] Most cases are preceded by a stressful event, and the typical electrocardiographic pattern involves ST-segment elevation in the precordial, lateral, and apical leads. Usually, there is a less pronounced increase in myocardial necrosis enzymes compared to other forms of ACS.[46] Coronary angiography demonstrating the absence of angiographically significant stenoses, combined with ventriculography documenting ventricular wall motion abnormalities, represents the diagnostic gold standard. The other differential element is the reversible nature of left ventricular dysfunction, which is accompanied by the characteristic absence of late gadolinium enhancement (LGE) on cardiac MRI. The prognosis is comparable to other forms of ACS.

Myocarditis.

Whether to include myocarditis among the possible causes of MINOCA is still a matter of debate. Some forms of myocarditis with a non-diagnostic clinical presentation and in the absence of a complete diagnostic workup may be mistakenly labeled as MINOCA. These diagnostic errors obviously have a significant impact on therapeutic and prognostic conclusions, as emphasized in a meta-analysis of five studies showing that 33 % of patients included in the MINOCA caseload had evidence of myocarditis on cardiac MRI.[47] Several authors believe that only certain forms of myocarditis can fall under the MINOCA category, particularly those involving microvascular rather than myocardial involvement. In myocarditis, myocardial edema can externally compress the microcirculation, contributing to the release of cardiac enzymes due to myocardial flow reduction. However, myocardial damage can also be directly caused by components of the immune system following viral infections. Acute myocarditis is predominantly caused by infection with Coxsackie virus, adenovirus, influenza viruses, or EBV. Myocarditis forms supported by PVB19 are characterized by dysfunction of the coronary microcirculation, resulting in vasoconstriction with consequent cardiac dysfunction.[48,49] Characteristic symptoms include chest pain, elevation of myocardial necrosis markers, and ST-segment alterations on ECG in the absence of significant vascular stenosis. The gold standard for the diagnosis of acute myocarditis is still endomyocardial biopsy; cardiac MRI is used for the diagnosis of viral myocarditis, which, as we have said, is most strongly associated with ACS.[50]

Criteria and diagnostic pathway of MINOCA (myocardial infarction with non-obstructive coronary arteries)

To formulate the diagnosis of MINOCA, three diagnostic criteria must be met.

Firstly, it is necessary to adhere to the criteria of AMI in accordance with the fourth universal definition:

- Detection of an increase or decrease in cardiac troponins (I or T, including high-sensitivity) with at least one value exceeding the 99th percentile of the reference limit value.
- Clinical evidence of infarction, demonstrated by at least one of the following:
- Symptoms of myocardial ischemia.
- New electrocardiographic changes suggestive of ischemia.
- Development of pathological Q waves.
- Evidence on imaging of new loss of viable myocardium or new alterations in regional contractility compatible with ischemic genesis.
- Identification of an intra-coronary thrombus through angiography or autopsy.

The other aspect necessary for diagnosis is the performance of coronary angiography. The angiographic examination must document the absence of lesions causing narrowing >50% compared to the uninjured epicardial coronary tract. The <50 % cut-off value has been arbitrarily defined and is subject to considerable inter- and intra-operator variability. For this reason, some authors have suggested the possibility of restricting diagnostic criteria to patients with completely normal coronaries on angiography, an occurrence that characterizes approximately half of MINOCA cases. However, this approach is not practicable for several reasons: firstly, because the presence of <50 % stenosis does not preclude thrombotic etiology or vasospasm, and secondly, because an angiographic finding of normality may still be associated with a significant atherosclerotic component, as documented by analysis with intracoronary imaging or coronary CT performed subsequently to coronary angiography in MINOCA-suspected patients. For these reasons, the authors of the ESC position paper considered it more appropriate to indicate a cut-off value of ≥50 % to exclude the diagnosis of MINOCA.

The third and final criterion for diagnosing MINOCA is the absence of specific alternative diagnoses such as myocarditis and pulmonary embolism.

Diagnostic pathway

The diagnostic pathway used to identify the underlying etiology of MINOCA is complex and based on the execution of various types of investigations, each with different accuracy and sensitivity (Fig. 2)

Clinical history, ECG, cardiac enzymes, echocardiography, coronary angiography, and ventriculography represent first-level investigations to identify the causes of MINOCA. Clinical findings may lead to suspicion of myocarditis (in case of fever or recent infections). Echocardiography may suggest embolic causes or Takotsubo disease, which will be confirmed by ventriculography. Ventriculography can also indicate an epicardial pattern, in the presence of regional kinetic anomalies limited to the territory of a single epicardial coronary vessel, or a microvascular pattern if the functional alteration involves a more extensive territory underlying a single vessel.

However, in many cases, second-level investigations are necessary to define the mechanism of MINOCA.

IVUS and, more recently, OCT are intracoronary imaging techniques widely used in the diagnosis of MINOCA, each with its characteristics and specificities. Table 2 compares the main differences between the two diagnostic techniques, which can highlight plaque rupture or erosion in 20–30 % of cases and can also be useful in suspected coronary dissection.[51]

Coronary vasomotor function tests (intra-coronary injection of Acetylcholine or Ergonovine) have shown to be safe and capable of diagnosing epicardial or microvascular spasm even in the acute phase.[52] If myocarditis is suspected, Cardiac MRI is essential both in the acute phase, to confirm the diagnosis, and for risk stratification. It may be useful to repeat the MRI during follow-up to more accurately assess ventricular function and response to therapy.[53] Cardiac MRI is the only method capable of demonstrating myocardial edema, which can contribute to myocardial ischemia and subsequent necrosis.

Transthoracic and transesophageal echocardiography, along with contrast agents, are the mainstays of diagnosis for cardiac embolism.[54]

Diagnostic confirmation and differential diagnosis

As previously mentioned, the mechanism responsible for myocardial damage in MINOCA is ischemic in nature. Therefore, it is necessary to exclude all causes, both cardiac and non-cardiac, that result in non-ischemic myocardial damage, both acute and chronic.

Clinical presentation often suggests various diagnoses, and it is not always possible to identify a certain etiological cause.

The ESC expert panel's position paper on MINOCA identifies MRI as a key examination in the diagnostic approach to this condition.

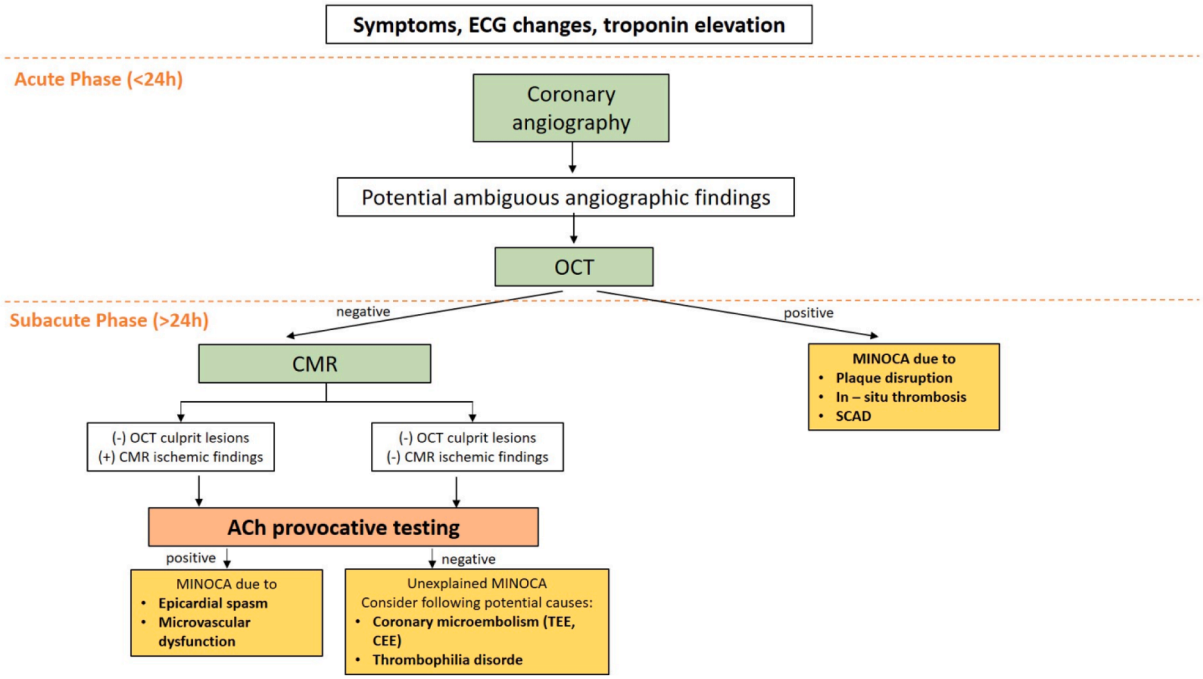

Fig. 2. Diagnostic alghorithm for MINOCA ACh, acetylcholine; CMR, cardiac magnetic resonance; ECG, electrocardiogram; LV, left ventricular; MICAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary arteries; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection.

Performing MRI allows diagnostic confirmation of MINOCA and identifies the underlying cause in 87 % of cases, while simultaneously excluding other pathologies in the differential diagnosis.[55]

The pattern and distribution of contrast medium in delayed acquisitions (LGE) allow differentiation between vascular and non-vascular causes:

- Sub-endocardial or transmural localization with territorial coronary distribution (ischemic pattern) is indeed the consequence of an ischemic mechanism.
- Intra-myocardial or sub-epicardial localization (non-ischemic pattern) recognizes other causes (e.g., myocarditis, cardiomyopathies, etc.).

However, approximately 8–67 % of MINOCA cases show normal findings on MRI, characterized by the absence of ventricular kinetic anomalies, edema, or LGE.[56] This may depend on various factors such as the time interval between the examination and the acute event, the age of the study population, the percentage composition of male/female gender, and the presence of modest diffuse fibrosis not identified with standard LGE sequences.

New signal mapping techniques of myocardial T1 and T2 introduced in recent years may certainly contribute to improving the ability to identify areas of pathological myocardium. Indeed, the presence of ischemic-pattern LGE has been reported in only 44 % of MINOCA patients analyzed with OCT. When MRI findings are normal, in the absence of another clarifying diagnosis, definitive diagnosis remains challenging for the clinician, and empirical treatment is often resorted to.[56–58]

Recent studies have focused on identifying and analyzing potential biomarkers to facilitate etiological diagnosis and prognostic stratification in ACS. A prospective Japanese study documented the diagnostic and prognostic value of leukocyte Rho-kinase activity in the context of vasospastic angina, while in the context of plaque erosion, a key role seems to be played by serum levels of metalloproteinase and activation of hyaluronic acid metabolism, as evidenced by increased hyaluronidase gene expression. Additionally, cystatin-C levels have been found to be higher in NSTEMI cases not associated with endoluminal thrombosis.[59–62]

Prognosis of MINOCA patients

Prognostic data on MINOCA are highly contrasting.[63] The Beltrame group shows that all-cause mortality at 12 months is lower in MINOCA compared to patients with myocardial infarction and obstructive coronary artery disease (4.7 % vs. 6.7 %).[64] However, a recent retrospective analysis of patients from the ACUITY study, involving 13,800 patients with moderate-to-high-risk ACS who underwent coronary angiography within 72 h, showed that compared to NSTEMI and CAD patients, MINOCA patients had a higher risk of one-year mortality (4.7 % vs. 3.6 %), although associated with an increase in non-cardiac deaths (2.1 % vs. 1.2 %), against a higher rate of recurrent myocardial infarction and repeated revascularizations in NSTEMI patients at one year.[65]

In the VIRGO study, conducted on 2690 patients focused on young presentations (<55 years), MINOCA had a comparable prognosis at 12 months compared to patients with MI-CAD and was more prevalent in women.[64–66] This study also highlighted that MINOCA patients have a higher short-term survival rate than patients with STE-ACS and a similar or worse long-term prognosis.[67]

Even more significant are the results obtained from the Swedish SWEDEHEART registry study,[68] conducted on 199,163 patients with first MI presentation, which showed that 23.9 % of MINOCA patients developed major adverse cardiovascular events (MACE) over 4 years of follow-up, with a total mortality rate of 14 %.

This contradiction in the published literature data may depend on the populations enrolled in the studies, the underlying mechanism, and the fact that there are high-risk subsets in MINOCA as described below.

High-risk subsets in MINOCA with epicardial mechanism

In cases of unstable plaque not evident on angiography but documented with IVUS/OCT, recent data suggest that plaque ruptures are associated with a worse prognosis than intact fibrous caps.[69] The severity of atherosclerosis is also important, being a predictor of worse prognosis in MINOCA as well as high levels of C-reactive protein (CRP) at admission.[70] Crea and Libby recently classified the mechanisms underlying AMI into:

- Inflammatory plaque ruptures, characterized by abundant macrophage infiltrate and inflammatory cells.
- Non-inflammatory plaque ruptures, where a mechanical trigger is the basis of the ruptures;
- Plaque erosions.
- Smooth plaques hyperreactive to vasoconstrictor stimuli. Among these, recent unpublished data suggest that inflammatory ruptures are at higher risk of recurrent events. Therefore, when inflammatory plaque rupture is found underlying MINOCA with evidence of local or systemic inflammation, follow-up should be particularly close due to the high risk of atherothrombotic recurrences.

For vasospastic forms, the abnormal response to Ergonovine or Acetylcholine testing is associated with a worse prognosis, both in relation to major events (such as death from any cause, cardiac death, re-hospitalization for acute coronary syndrome) and in relation to quality of life. The negative prognostic value associated with positive provocative tests seems largely related to the induction of epicardial coronary spasm.

For spontaneous dissections, in-hospital and long-term survival are excellent, despite the reported high risk of acute recurrence (27

% / 5 years).[71]

High-risk subsets in MINOCA with microvascular mechanism

Regarding microvascular spasm, although the prognosis is good in the short term, there are two aspects to consider. The first concerns anginal symptoms that may recur, compromising the patient's quality of life (up to 36 %, despite the use of Calcium Channel Blockers).[53] The second aspect concerns long-term prognosis. Microvascular spasm is an expression of microcirculatory dysfunction that numerous invasive and non-invasive studies have associated with a non-benign long-term prognosis.[72] Microcirculatory dysfunction is indeed a negative predictor of adverse cardiovascular events (death, myocardial infarction) and non-cardiac mortality, as an expression of systemic risk.[73]

Regarding myocarditis, a similar infarct-like pattern has been associated with a better prognosis than non-infarct-like presentation, and evidence of LGE (late gadolinium enhancement) as a predictor of adverse prognosis.

Management of MINOCA patients

As previously addressed, the term MINOCA should constitute a "working diagnosis," aimed at identifying underlying causes to optimize treatments and promote prevention of further infarction events. We have also discussed the fundamental role of cardiac magnetic resonance (CMR) in allowing us to arrive at a definitive diagnosis in about 90 % of cases. However, only 44 % of MINOCA patients present with an ischemic pattern on CMR, even when plaque destruction has already been documented on OCT.[74,75]

In three observational studies, it has been shown that treatment with ACE inhibitors and ARBs has beneficial effects on the outcome of these patients.[76,77] The SWEDEHEART study, mentioned in the previous section, showed a 23 % reduction in MACE in patients treated with statins, an 18 % reduction in patients treated with ACE inhibitors and ARBs, and a 14 % reduction in patients treated with metoprolol (a beta-blocker). No significant reduction in MACE has been demonstrated with dual antiplatelet therapy (DAPT).[78]

According to a recent statement from the AHA (American Heart Association), the optimal strategy for correct management of patients with MINOCA should include:

- Supportive care in emergencies.
- A working diagnosis approach for patient evaluation.
- Cardioprotective therapy regardless of the underlying cause of MINOCA.
- Targeted therapies.

The AHA guidelines primarily focus on evidence of targeted therapies for the cause in the overall treatment of MINOCA, particularly for MINOCA with ischemic presentation.[78] Any patient with atherosclerosis, modifiable risk factors for CAD (such as smoking, hypertension, diabetes mellitus, and hyperlipidemia), should be aggressively treated through aspirin intake as a treatment for the prevention of atherosclerotic plaque erosion, given the similar pathogenetic mechanism to that of AMI-CAD. Recent studies[79] conducted on patients with AMI have also highlighted an increased benefit from the intake of P2Y12 receptor inhibitors concurrently with aspirin.

For MINOCA patients with vasospastic angina, calcium channel blockers and nitrates are used as first-line treatment. In case of refractory forms of vasospastic angina, a combination therapy of dihydropyridine and non-dihydropyridine calcium channel blockers or the addition of nicorandil (a potassium channel activator) can be considered.

In the group of patients with MINOCA due to microcirculatory dysfunction, dipyridamole and ranolazine are indicated, promoting vasodilation. Potential benefits can also be obtained from drugs such as imipramine and aminophylline. Physical exercise for cardiac rehabilitation plays a very important role in the management of cardiovascular diseases, as it reduces both mortality and possible adverse cardiovascular events. He et al[79] have demonstrated that engaging in physical activity three times a week, for about 20–30 min, improves the survival and health of MINOCA patients; therefore, it becomes essential to empower the patient about the benefits of consistent physical exercise.

Currently, there are no studies on the treatment of spontaneous coronary artery dissections (SCAD), however, an observational study recommends the use of beta-blockers. The use of DAPT in patients with SCAD is still controversial as it carries an increased risk of bleeding. However, a study has suggested the possibility of administering clopidogrel to SCAD patients if the intimal lesion is in a prothrombotic stage.[80] From a study conducted on 72 patients with Takotsubo syndrome, it emerged that these patients benefit from a combination therapy of anti-thrombotic and heart failure therapy for the first two months after the acute event. According to the InterTak group, if coronary atherosclerosis is also present, aspirin and statins should be added.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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