ARGENTINE SOCIETY OF CARDIOLOGY

MINOCA Consensus Statement
Myocardial Infarction with Nonobstructive Coronary Arteries / Abridged version

Consensus for the diagnosis and treatment of MINOCA
Multidisciplinary Argentine Society of Cardiology Working Group
(Full version, see SAC consensus area)

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Abbreviations

ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitors
ACh	Acetylcholine
ACS	Acute coronary syndrome
ADA	Anterior descending artery
AHA	American Heart Association
AMI	Acute myocardial infarction
ARB	Angiotensin II receptor blocker
ASA	Acetylsalicylic acid/aspirin
CA	Coronary angiography
CAD-AMI	Coronary artery disease acute myocardial infarction
CCTA	Coronary computed tomography angiography
CE	Coronary embolism
CMR	Cardiac Magnetic Resonance Imaging
CN	Calcified nodules
COVID	Coronavirus disease
CFR	Coronary flow reserve
CXA	Circumflex artery
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulants
ECG	Electrocardiogram
Ergo	Ergonovine
ESC	European Society of Cardiology
FFR	Fractional flow reserve
GLS	Global longitudinal strain
HIT	Heparin induced thrombocytopenia
IC	Intracoronary
IM	Intramuscular
IV	Intravenous
IVUS	Intravascular ultrasound
LV	Left ventricle
MBF	Myocardial blood flow
MINOCA	Myocardial infarction with nonobstructive coronary arteries
MVD	Microvascular dysfunction
NIRS-IVUS	Near-Infrared spectroscopy intravascular ultrasound
NSTEMI	Non-ST-segment elevation acute myocardial infarction
NTG	Nitroglycerin
OCT	Optical coherence tomography
PE	Plaque erosion
PET	Positron emission tomography
PR	Plaque rupture
QCA	Quantitative coronary analysis
RCA	Right coronary artery
SCAD	Spontaneous coronary artery dissection
SPECT	Single photon emission computed tomography
STEMI	ST-segment elevation acute myocardial infarction
TCFA	Thin-cap fibroatheroma
TEE	Transeophageal echocardiography
Tn	Troponin
TTE	Transthoracic echocardiography
TTP	Thrombotic thrombocytopenic purpura
VH	Virtual histology
VH-IVUS	Virtual histology intravascular ultrasound
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VP	Vulnerable plaque

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Summary

INTRODUCTION

1.1 Consensus objective

The objective of this consensus is to guide cardiologists in our country in the recognition of people who suffer from an acute myocardial infarction (AMI) with unobstructive coronary artery disease and to recommend tools to identify its possible causes. Several working groups belonging to international scientific societies (2016 ESC, 2019 AHA, and 2019 Dutch Group) (1-3) have established the different etiologies and differential diagnoses, but have not given specific recommendations.

1.2 Nomenclature

The guideline nomenclature recommended by the Argentine Society of Cardiology is as follows:

Recommendation class: It estimates the effect size of a treatment based on the risk/benefit, as well as the evidence or level of agreement in which a given procedure is effective, ineffective, or dangerous.

Recommendation class. Classification	
Class I	Evidence and/or general agreement that a certain diagnostic procedure or treatment is beneficial, useful and effective.
Class II	Conflicting evidence and/or divergence of opinion about the usefulness or efficacy of the procedure/treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less established by evidence/opinion.
Class III	Evidence or general agreement that the treatment is not useful/effective and, in some cases, may be harmful, and its use is discouraged

Level of evidence: estimates the certainty and precision of the procedure or treatment effect.

Level of evidence. Classification	
Class A	Data from multiple randomized clinical trials or meta-analyses. Consistency in direction and magnitude of effect
Class B	Data from a single randomized clinical trial or non-randomized studies.
Clase C	Expert opinion consensus or from small studies.

1.3 Definition of infarction. "The revolution of troponins"

The emergence of troponins (Tn) as more sensitive and specific cardiac biomarkers prompted the collaboration of the European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the American Heart Association (AHA) to redefine acute myocardial infarction (AMI) using a clinical and biochemical approach. Patients with elevated and decreased Tn, with at least one value above the upper normal limit in the context of myocardial ischemia, should be classified as AMI. Based on these new concepts and findings, the universal definition of infarction was created and published for the first time in 2000. This regulation encompasses all types of AMI but had to be redefined four times given the biomarkers lack of specificity to differentiate the ischemic cause, non-ischemic myocardial injury or non-cardiac cause.

Currently, the 4th definition of AMI is in force, emphasizing that, in addition to Tn kinetics, some of the following elements should be associated to define AMI and differentiate myocardial injury from myocardial ischemia: (4)

- Symptoms (angina, anginal equivalent).
- Electrocardiographic changes (ST-segment elevation or depression, changes in the T wave or new Q waves).
- Imaging evidence with loss of viable myocardium or regional wall motion abnormalities.
- Identification of coronary thrombosis by angiography or pathological anatomy.

Based on these characteristics, AMI has been classified into 5 types

Type 1

Plaque rupture (PR) or plaque erosion (PE) with atherothrombotic occlusion (STEMI)

Plaque rupture or PE without atherothrombotic occlusion (NSTEMI)

Type 2

Imbalance between oxygen supply and demand, but without thrombosis.

Previous coronary artery disease.

Epicardial and microvascular coronary artery spasm

Non-atherosclerotic coronary dissection.

Coronary embolism

The remaining types of infarcts are related to sudden death, coronary angioplasty, and myocardial revascularization surgery.

1.4 MINOCA

The 4th definition of AMI incorporates the acronym MINOCA, which represents acute myocardial infarction with unobstructive coronary arteries (stenosis <50%) (Table 1). This entity is not new: the finding of AMI with "normal coronary arteries" has been known for more than 50 years.

Tabla 1. Criteria for the definition of MINOCA. 4th universal definition of AMI

Angiographic clinical syndrome whose pathophysiology is myocardial ischemia
1. Acute myocardial infarction
Increase and decrease of troponins with at least one value above the 99th percentile upper reference limit,
plus at *least one of the following criteria*:
a. Myocardial ischemia symptoms
b. New ischemic electrocardiographic changes
c. Pathological Q wave development
d. Imaging evidence with loss of viable myocardium or new regional wall motion abnormalities.
e. Identification of coronary thrombosis by angiography or pathological anatomy
2. Non-obstructive epicardial coronary arteries:
Defined as the absence of obstructive coronary artery disease (≥50%) of any epicardial coronary vessel
- Normal epicardial coronary arteries
- Mild intraluminal abnormalities (stenosis <30%)
- Moderate atherosclerotic coronary lesions (stenosis >30% and <50%)
3. Alternative diagnoses of myocardial injury that rule out MINOCA
- Sepsis, pulmonary embolism, myocarditis, and aortic dissection, among others

MINOCA constitutes a clinical angiographic syndrome that, by definition, has different causes, but whose pathophysiology must be myocardial ischemia. According to the 4th universal definition the presence of AMI and nonobstructive coronary artery disease (<50% or normal coronary arteries) is necessary to diagnose MINOCA. Regarding the causes, it can be due to type I (PR or PE) or type II (spasm, coronary dissection or microvascular disease) infarction, and in this context, they must be differentiated from oxygen supply and demand imbalances (hypertensive crisis or tachyarrhythmias). The differential diagnosis with disorders or direct damage to the myocardium, such as myocarditis or Takotsubo disease, which can mimic MINOCA, is also very important. In this sense, the term MINOCA may also be considered as an operational classification that enables triggering algorithms to confirm the infarction or differentiate it from a specific myocardial disease. (Figures 1-3). This is how the term *working diagnosis* has been incorporated in the literature, indicating an exhaustive work for the diagnosis of MINOCA, ruling out hidden occlusions, coronary dissection or non-cardiac causes. (4)

Finally, the causes that can produce MINOCA run through the entire coronary tree, including from epicardial coronary arteries to the microcirculation. The latter has the characteristic of representing 70% of myocardial vascular resistance and cannot be observed in coronary angiography (CA), since its diameter is less than 0.5 mm. Briefly, it is possible to consider the following pathologies that can cause MINOCA:

a) Epicardial coronary arteries
- Nonobstructive atherothrombotic accident
- Coronary spasm
- In situ thrombosis
- Coronary embolism
- Spontaneous coronary dissection

b) Coronary microcirculation
- Microvascular spasm
- Microvascular dysfunction

The complication of an atherosclerotic plaque can produce MINOCA as a consequence of total obstruction caused by lysis or distal embolization procedure. In patients with normal coronary arteries, we can only know if the cause is due to spasm if it occurs spontaneously or is induced by vasoreactivity tests. Thrombosis, em-

bolisms, and dissection can present with obstructions <50%, and a differential diagnosis should be made with plaque accidents, or else they may go undetected in CA, since they may occlude secondary or distal branches. Upon suspicion of this situation, CA should be reviewed again to identify wall motion abnormalities to establish which branch has been compromised, and magnetic resonance imaging is the gold standard to detect the infarcted area (working diagnosis). A microvascular abnormality can be the cause of MINOCA, both due to spasm or inadequate vasodilation; to confirm this situation, we must also resort to different invasive or non-invasive tests. Throughout this consensus, each of these topics is thoroughly developed

2. MINOCA EPIDEMIOLOGY: prevalence, risk factors and prognosis

In the 1980s, De Wood reported that approximately 10% of patients who presented with myocardial infarction did not have obstructive coronary disease of the epicardial arteries that could justify the event. (5) A systematic review by Pasupathy et al. indicates a prevalence of MINOCA of 6%, with a wide range from 1% to 15%. (6) This is mainly due to differences in the study populations and heterogeneity in its definition.

Regarding MINOCA etiology, studies with cardiac magnetic resonance imaging (CMR), optical coherence tomography (OCT) and vasoreactivity tests begin to suggest the most frequent causes. Using a combination of CMR and OCT intravascular evaluation, the etiology of ischemia can be defined in 57.5% to 85% of cases. The most frequent causes are plaque accidents (35% rupture, 30% erosion and 2.5% calcium nodule) and, in a smaller percentage of patients, spontaneous coronary dissection and isolated thrombosis. (7,8) Moreover, in a study in which a vasoreactivity test was performed in patients without evident etiology, the result was positive in 46%of cases; with 65% attributable to epicardial artery spasm and 35% to microvasculature spasm. (9)

The prognosis of patients presenting with MINOCA depends on the underlying cause and is currently under very active investigation. The systematic review by Pasupathy et al. reported a better prognosis in patients with MINOCA compared with atherosclerotic coronary artery disease acute myocardial infarction (CAD-AMI) with in-hospital mortality of 1.1% vs. 3.2% (p=0.001) and mortality at 12 months of 3.5% and 6.7% (p=0.003), respectively. (6) On the other hand, the VIRGO registry, showed similar evolutions between patients with and without epicardial disease, with mortality of 1.1% and 1.7% at 1 month (p=0.43) and 0.6% and 2.3% at 12 months (p=0.68), respectively. Furthermore, there is a substantial risk of event recurrence during the follow-up of MINOCA patients, which is higher than that observed in the general population without cardiovascular disease. (10) Approximately 25% of patients with MINOCA experience angina in the following 12 months, a frequency similar to that reported in patients with CAD-AMI. (11)

3. INVASIVE STUDIES IN MINOCA (Table 2)

3.1 Transient coronary occlusion produced by rupture, erosion or the presence of calcified nodules. OCT and IVUS

Intravascular thrombosis is a central element in the development of acute coronary syndromes (ACS). Sometimes it is a dynamic process, with spontaneous occlusions and reperfusions.

The substrates on which this thrombosis process develops are usually PR, PE and the presence of calcified nodules (CN).

Plaque rupture is the predominant lesion, followed by PE, with variable incidence depending on whether they are histopathological studies or those performed in vivo with OCT. (12,13)

The histopathological differences between a ruptured plaque and an eroded plaque are described in Table 1 of the Supplementary Material.

Nodular calcification is the protrusion of the calcium nodule into the vessel lumen; in angiography, it can simulate intraluminal thrombosis; in ultrasound and OCT, the aspect is that of an intravascular convex mass with an irregular surface. (14)

The methods for obtaining intravascular images in vivo have allowed expanding the understanding related to the ACS pathophysiology in general and of MINOCA in particular.

Intravascular ultrasound (IVUS) is currently the most widely used method and allows obtaining a two-dimensional image of the artery, with penetration of up to 10 mm and spatial resolution of 100 to 200 microns. It provides a good characterization of the plaque, but limits its usefulness in the diagnosis of the accident phenotype responsible for the thrombosis. Virtual histology (technologies such as VH-IVUS- or iMap) uses the radiofrequency spectral analysis of IVUS to create a tissue map of the plaque with the ability to identify the necrotic nucleus, fibroadipose area, fibrous area and calcium.

Optical coherence tomography has higher spatial resolution (10-20 microns), but less penetration, and requires blood displacement during acquisition. Its higher resolution makes it the method of choice for the characterization of vulnerable and complicated plaques in ACS. The complete comparative description of the techni-

cal characteristics and sensitivity of OCT and IVUS to detect atherosclerotic lesions can be seen in Tables 2 and 3 of the Supplementary Material.

In the International Women's Heart Attack Research Program (HARP) study, women with AMI without angiographically significant lesions were prospectively evaluated with CMR and OCT. Optical coherence tomography was able to identify a possibly culprit lesion in 46% of cases and the combination of OCT and CMR identified the probable cause of MINOCA in 84.5% of cases. (8)

In the EROSION study, the authors suggest that when the cause of the ACS is PE diagnosed by OCT, a stentless dual antiplatelet therapy (DAPT) may be useful in patients in whom, initially, the stenosis is less than 70%. (15)

More recent evidence suggests a lower coronary vulnerability in patients with STEMI and a responsible lesion with PE, which could explain, in part, the better long-term evolution of these patients compared with those with a culprit lesion due to PR. (16)

3.2 Spontaneous coronary dissection

Spontaneous coronary artery dissection (SCDA) is a rare cause of ACS, characterized by non-traumatic or iatrogenic separation of the coronary artery wall layers. It presents with a calculated prevalence of 1.7% to 4%, although in women under 50 years of age, it could represent 25% or more of the cases. (17-19) A significant percentage of these patients have moderate stenosis with TIMI 3 flow.

Angiographic diagnosis is not always simple and, in some cases, the arteries may appear pseudonormal. In a recent series, the initial presentation as intramural hematoma was the most frequent cause (62%) and TIMI 3 flow was present in 64% of cases. (20)

Intravascular imaging techniques (IVUS-OCT) can confirm the diagnosis in doubtful cases, but must be performed with extreme caution due to the possibility of worsening the trauma on a weakened arterial wall.

3.3 Coronary embolism

Coronary embolism (CE) can be the cause of ACS. A 12-year review of coronary angiographies in patients with AMI suggests that it could have a prevalence of up to 3% (21) and its incidence in patients with MINOCA is unknown.

The differential diagnosis with thrombosis on a disrupted plaque is difficult. **Major and minor criteria** suggesting the embolic etiology have been postulated. (21) (Table 4 of the Supplementary Material).

3.4 Coronary artery spasm

The definition of coronary spasm has been internationally standardized by the COVADIS group (Coronary Vasomotion Disorders International Study Group). Conceptually, it can be defined as the intense vasoconstriction of an epicardial coronary artery (>90%) that compromises myocardial flow, accompanied by angina pectoris and transient ischemic changes in the ECG that subside with the use of nitrates. (22) (Table 5 of the Supplementary Material).

The spasm can be caused by hyperactivity of the vascular wall to endogenous stimuli, but also, to exogenous incentives (cocaine or methamphetamines), and is currently considered to be multifactorial. (23)

A prolonged vasospasm can cause MINOCA. In a study where a vasoreactivity test was performed in patients with MINOCA without evident cause, the test was positive in 46% of cases (65% epicardial artery spasm and 35% microvascular spasm), which suggests that it is a very prevalent mechanism in this disease. (9)

The diagnosis should be suspected in patients with repeated episodes of angina at rest, with a specific pattern (usually nocturnal), especially with ECG showing transient ST-segment elevation, who respond to nitrates. Unfortunately, this occurs in the minority of cases and provocative coronary artery spasm testing must be used to reach a diagnosis. These tests can be safely performed with intracoronary (IC) acetylcholine (ACh) or ergonovine (Ergo) injection, as highlighted in a systematic review of 10 studies involving 9444 patients, where no deaths were reported and there was a low incidence of complications, both major (ventricular tachycardia or ventricular fibrillation) and minor (transient bradycardia, advanced atrioventricular block or paroxysmal atrial fibrillation). Compared with Ergo, ACh showed a significantly higher rate of both major (1.09% vs. 0.15%; $p < 0.001$) and minor (5.87% vs. 2.36%; $p < 0.001$) complications. (24)

3.4.1 Coronary microvascular dysfunction. Microcirculation spasm

Microcirculatory disorders, known as microvascular dysfunction (MVD), can be the cause of MINOCA, both due to spasm as inadequate vasodilation, and can be evidenced in the hemodynamic laboratory with an endothelium-dependent or endothelium-independent test, according to the response to ACh (nitric oxide release from normal endothelium) or adenosine (A2 receptor stimulation of the vascular wall smooth muscle), respectively. (25) A standardized definition of microvascular angina that includes patients with angina pectoris, unobstructed coro-

nary arteries, and impaired coronary flow has been established. (26) (Table 6 of the Supplementary Material).

The diagnosis of microvascular spasm is indirect, since coronary microcirculation cannot be visualized due to its small diameter (500 μm). If the use of ACh or Ergo testing induces the emergence of myocardial ischemic-like ECG changes, angina or elevated lactic acid in the coronary sinus, without visible abnormality of the epicardial artery blood flow, diagnosis of microvascular spasm is assumed.

Clinical disorders of coronary MVD have been described, to a large extent, in patients presenting with stable angina. (27) Abnormal coronary flow reserve (CFR) is determined by the hyperemic response to vasodilator stimuli, such as adenosine IC injection.

Microcirculation disorders can also be measured by slow coronary flow, an angiographic phenomenon that can occur spontaneously, and is characterized by a delay in the passage of angiographic contrast; therefore, to fill an epicardial coronary vessel at rest, three or more heartbeats (> 25 frames to completely stain with contrast a coronary artery) should pass. (28)

In clinical practice, evaluation of epicardial coronary artery spasm and MVD might be more appropriate using combined tests.

Coronary MVD can be detected in 30% to 50% of patients with stable chronic angina without significant coronary obstructions at CA; (27) however, its incidence as a cause of MINOCA is unknown.

3.4.2 Invasive provocative testing for coronary spasm

Endothelium-dependent vasodilation can be stimulated in different ways, but the most common is ACh infusion, which, under normal conditions and with a healthy endothelium, produces vasodilation by nitric oxide release through muscarinic receptors. When there is endothelial damage or nitric oxide synthase is blocked, the artery responds to ACh with vasoconstriction by stimulation of muscarinic receptors in smooth muscle, without antagonism due to the absence of nitric oxide. Ergovine works through serotonergic receptors. Different mediators can have the potential to cause different responses. Goto et al. demonstrated a similar response with both drugs in 134 vessels of 171 patients with stenosis <50%. Concordance was 94% in all vessels. The non-concordance rate of the right coronary artery was significantly higher than that of the left coronary artery (10% vs. 4%; p <0.01). However, ACh caused more diffuse and distal spasms and Ergo caused focal and proximal ones.

The sensitivity of IC Ach injection was 90% in variant angina and the specificity reached 99%. Multivessel coronary artery spasm was often observed. (29) Acetylcholine spasm provocative testing replaced intravenous injection of Ergo as the standard test for the induction of coronary artery spasm in catheterization laboratories in Japan. Intracoronary ACh injection is the gold standard for diagnosing variant angina. This method is used to document coronary artery spasm.

3.4.3 Contraindications for the performance of coronary spasm provocative testing

- Stenosis of the left main coronary artery (>50%).
- Three-vessel coronary disease.
- Two-vessel disease with total occlusion.
- Heart failure (New York Heart Association class III or IV).
- Kidney failure (creatinine >2.0 mg/dl).
- Severe bronchial asthma.
- In cases of spontaneous spasm.
- When isosorbide dinitrate has been used to relieve spasms in the coronary artery examined.
- Pregnant women.
- Patients with uncontrolled hypertension.

When using the radial approach to perform a CA, the use of long introducers is recommended to avoid spasm.

A “washout” period of 2 days or more is also suggested for any long-acting calcium and nitrate channel blocker, whenever possible, for greater diagnostic accuracy.

The study requires signing an informed consent.

3.4.4 Interpretation of coronary spasm provocative testing

Possible outcomes:

1. Negative test with vasodilator response: vasodilation without symptoms or changes in the electrocardiogram; normal endothelium.
2. Negative test with vasoconstrictor response: vasoconstriction without symptoms or changes in the electrocardiogram; indicative of endothelial dysfunction, especially with the initial dose.
3. Positive test for epicardial spasm, requires the following three criteria:
   - Reproduction of symptoms.
   - Electrocardiographic changes suggestive of ischemia, usually 0.1 mV ST-segment elevation or depres-

sion. The emergence of negative U wave has also been described.
- Spasm ≥90% in the luminal diameter of the same arterial segment with respect to baseline value (with previous nitroglycerin administration); it can be focal, multisegmental, or diffuse.

4. Positive test for microvascular spasm: symptoms and electrocardiographic changes (same as above), but without visualization of epicardial coronary spasm.
   Formula to measure the stenosis diameter due to coronary vasospasm:
   Stenosis diameter=100 - [(ACh-Ergo vasoconstriction/post-NTG diameter) x 100]. Positive result ≥90%. (30)
   Use of automated quantitative coronary analysis (QCA) of the vessel diameter is recommended.

3.4.5 Acetylcholine and ergonovine testing. Protocol for their use (see Supplementary Material)

3.4.6 Safety of coronary spasm provocative testing

Performed by experienced groups, Ach and Ergo testing is safe, and in large series with more than 2500 patients, no major complications have been reported. (31)

In a meta-analysis of several studies with more than 6000 procedures, the rates of major (ventricular arrhythmias, need for cardiopulmonary resuscitation or infarction) and minor (symptomatic bradycardia, transient atrioventricular block, onset of atrial arrhythmias or air embolism) complications were 1% and 6%, respectively, with no recorded patient death. (24) (Table 11 of the Supplementary Material).

Table 2. Recommendations for conducting invasive studies in MINOCA

Recommendation	Class	Level of evidence
Perform ventriculography in the initial CA to assess wall motion when not evaluated by another method and there are no contraindications (heart or kidney failure).	I	B
Perform IVUS or OCT in patients with suspected MINOCA at initial diagnostic catheterization to identify PR, PE, or thrombosis. (15) (center with availability).	IIa	B
Perform IVUS or OCT to identify PR or PE in patients in whom CMR suggests infarction attributable to epicardial vessel involvement. (14,15).	IIa	B
Due to its higher definition, OCT is preferable to IVUS for the characterization of coronary endothelium. (32)	IIb	B
Perform IC vasoreactivity test in patients with suspected coronary vasospasm, ruling out other causes of MINOCA [spontaneous coronary artery dissection (SCAD), thrombosis, or embolism]) 48 h after the index event. (15)	IIa	B
Do not perform vasoreactivity test with LV Ejection fraction <35% or significant left coronary trunk disease (left main coronary artery >50% or a main vessel >70%).	III	C

4. NON-INVASIVE STUDIES IN MINOCA (Table 3)

4.1 Echocardiography and cardiac color Doppler in the evaluation of MINOCA

Due to its wide availability, relatively low cost, and absence of contraindications, transthoracic echocardiography (TTE) can be used in the initial evaluation of the patient with suspected ACS in the emergency services. (33) The main objective of the study is aimed at detecting myocardial left and right ventricular wall motion disorders (both regional and global) suggestive of ischemia or necrosis for the differential diagnosis with myocarditis, Takotsubo, cardioembolism and non-coronary causes, among others.

4.1.1 Coronary microcirculation assessed by Doppler

In patients with MINOCA, evidence of MVD establishes the possible cause of ischemia. From an echocardiographic point of view, coronary circulation can be comprehensively assessed by measuring CFR. (26) This results from the ratio between diastolic coronary flow velocity at maximum hyperemia and at baseline condition, and a value ≥2 is considered normal. It is carried out with high feasibility (greater than 95%) in the middle/distal portion of the anterior descending artery (ADA), given its proximity to the thoracic wall, and may also be performed on the posterior descending artery (60%) and the obtuse marginal artery (circumflex branch) in approximately 40% of the examined patients. The induction of hyperemia is carried out with adenosine or dipyridamole. It should be noted that this evaluation does not discriminate between macrovascular and microvascular disease. Microvascular dysfunction diagnosis is established when there is a reduction in CFR and an undervalued epicardial coronary lesion. (34)

Once the acute condition is over, patients with MVD usually present a stress echo response pattern consisting of angina, electrocardiographic changes, absence of wall motion abnormalities and eventual CFR involvement. Lack of myocardial wall motion abnormalities is a consequence of limited and possibly patchy sub-endocardial malfunction, which does not reach a critical mass to produce hypokinesia. (35) It has been postulated that speckle tracking longitudinal and circumferential strain of the different myocardial strata may suggest microvascular ischemia in patients with dipyridamole stress echo without wall motion disorders, but with electrocardiographic signs of ischemia and symptoms. (36)

Table 12 of the Supplementary Material summarizes the advantages and limitations of echocardiographic CFR evaluation.

4.1.2 Echocardiography in the study of vascular spasm

In those patients in whom coronary vasospasm is suspected as a cause of MINOCA, it is possible to perform a non-invasive study by echocardiography using different stresses: hyperventilation, hyperventilation combined with exercise, and hyperventilation combined with cold.

The stress echo test with intravenous Ergo is not endorsed in the main clinical recommendation guidelines due to dread of complications, which can eventually be serious, especially refractory coronary spasm. (37)

4.2 Assessment of microvascular coronary dysfunction with nuclear medicine

A substantial proportion of symptomatic patients in the context of non-obstructive epicardial disease present MVD as functional substrate, which cannot be diagnosed by studies that provide anatomical information. (38,39) Resorting to nuclear cardiology, European guidelines recommend the evaluation of CFR by positron emission tomography (PET), with class IIb recommendation, level of evidence B, as a surrogate for MVD. (40) More recently, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines consider as appropriate the evaluation of microcirculation by PET in patients with non-obstructive disease and symptomatic precordial pain. (41) Positron emission tomography in conjunction with perfusion tracers (N-13 ammonium and Rb-82) allows assessment of myocardial perfusion, ventricular function, and quantification of myocardial blood flow (MBF) in milliliters per gram per minute. This absolute flow quantification is performed globally, by coronary vascular territory and by left ventricular segment. (42) The evaluation of MBF during pharmacological stress (adenosine, dipyridamole, regadenoson) and at rest allows the calculation of CFR (CFR=hyperemic MBF/resting MBF). Coronary flow reserve is a parameter that evaluates the effects of epicardial coronary artery disease, diffuse atherosclerotic disease and MVD on myocardial tissue perfusion. Preserved CFR is considered when the value is ≥2.5; when it is 2-2.5 it is considered as a gray area and when it is <2 it is assumed as pathological. (43) The demonstration of a decrease in CFR is today part of the comprehensive diagnosis of microvascular angina in patients with chest pain. (26)

Sympathetic stimulation induced by the cold pressor test preferably indicates the vasodilation of the endothelium-dependent microcirculation. (42) Absolute quantification of MBF at rest and cold could be useful to unmask microvascular spasm as a cause of chest pain in patients with non-obstructive CD. An increase in MBF greater than 50% in response to cold indicates a preserved endothelial function. (42)

The conventional relative myocardial perfusion technique with single-photon emission computed tomography (SPECT) at rest, cold, and dipyridamole provides very little diagnostic information in most patients with microvascular angina and is not recommended. (42,44)

Given the possibility of performing an absolute MBF quantification study and calculate CFR or measure the response of MBF to cold, we recommend performing these studies in those patients with suspected microvascular dysfunction as a cause of MINOCA, or who present persistent chest pain, despite optimal medical treatment. (45)

4.3 Diagnosis of MINOCA with magnetic resonance imaging and coronary angiography

In patients with presumptive diagnosis of MINOCA, CMR imaging allows a diagnostic approach in 70% of cases; the rest have normal studies. On the other hand, it should be noted that the patient with MINOCA who presents a normal CMR has a good long-term prognosis. (46)

Cardiac magnetic resonance imaging allows evaluating wall motion abnormalities in cine sequences, the presence of myocardial edema in T2-weighted sequences, and the manifestation of inflammation and fibrosis at the myocardial level in late gadolinium enhancement (LGE) sequences. T1 mapping images enable injury and diffuse fibrosis assessment, and T2 mapping images are more accurate for the quantification of edema than traditional T2 sequences. (47)

It is convenient to carry out T2-weighted sequences early, within 2 weeks of the onset of symptoms, before the myocardial injury resolves or reverses, in order to increase the diagnostic performance, mainly in myocarditis and Takotsubo syndrome. (48) The presence of LGE and its different distribution patterns at the myocardial

level provide the best diagnostic performance of CMR. (1,48)

Coronary computed tomography angiography (CCTA) would be useful when there are doubts about the presence of atherosclerosis or coronary artery dissection, as well as to assess the extent and characterization of coronary lesions in patients with MINOCA. (3) Non-invasive fractional flow reserve (FFR) assessment is also possible by CCTA. (49) Computed tomography angiography findings could select patients suitable for invasive techniques such as OCT or IVUS and define the nature of MINOCA. (50)

4.3.1 Acute myocardial infarction

Ischemic lesions are recognized by the presence of wall motion abnormalities (hypokinesia, akinesia, or dyskinesia), edema, and subendocardial or transmural LGE in segments related to a coronary territory. (51) Similarly, in the occurrence of lesions with embolic characteristics, the presence of emboligenic sources, such as patent foramen ovale, papillary fibroelastoma and myxoma, should be excluded. (52)

4.3.2 Myocarditis

Myocarditis represents 27-33% of patients with suspected diagnosis of MINOCA. (48,53) The modified Lake Louise criteria for the diagnosis of myocarditis with the incorporation of T1 and T2 mapping sequences reinforce the role of CMR imaging, with sensitivity and specificity >90%. (54,55)

In T2- weighted sequences and T2 mapping, edema can be localized or diffuse. Diffuse edema may not be visually discernible; therefore, a quantitative intensity signal analysis of the cardiac and skeletal muscle is recommended, considering as pathological a value >1.9 of the ratio between them or by means of a T2 mapping sequence. (56) It is advisable to perform early T2 edema sequences, within 2 weeks, in order to increase the diagnostic yield, since the presence of edema is a phenomenon that disappears with the condition resolution. (48)

Late gadolinium myocardial enhancement manifests with two common presentation patterns, intramyocardial with septal predominance, and epicardial/intramyocardial, generally patchy at the level of the left ventricular lateral wall. (54) As a general rule, the subendocardium is not compromised in patients with myocarditis, a fact that clearly differentiates it from fibrosis, which is characteristic of myocardial infarction. (56) T1 mapping sequences show myocardial signal prolongation in areas of myocarditis injury. (55)

4.3.3 Takotsubo

Takotsubo syndrome represents 9-11% of patients with initial MINOCA diagnosis. (48,57) In CA sequences, hypokinesia or akinesia of the middle and apical segments associated with hyperdynamic basal segments is a Takotsubo syndrome characteristic. Another distinctive feature is the absence of perfusion defects at rest and with LGE. (58-60)

Table 3. Recommendations for conducting non-invasive studies in MINOCA

Recommendation	Class	Level of evidence
Perform TTE in patients with MINOCA, in order to assess the presence of regional and global wall motion disorders in both ventricles and to assess alternative diagnoses (cardioembolism, cardiomyopathies, and acute aortic syndrome, among others). (33)	I	B
Perform transesophageal echocardiography (TEE) when cardioembolic etiology is suspected as the cause of the MINOCA condition and the TTE study is not conclusive in this regard.	I	B
In patients with MINOCA and suspected microvascular dysfunction, noninvasive assessment of CFR by TTE is a reasonable option.	IIa	C
In patients in whom vasospasm is suspected as a cause of MINOCA, a stress echocardiogram with hyperventilation and/or cold may be used to confirm this diagnosis.	IIa	C
In patients with MINOCA or who continue with episodes of chest pain, despite optimal medical treatment, PET or SPECT-CZT test (SPECT based on cadmiun-zinc-telluride) induced by intravenous vasodilators (dipyridamole, adenosine, regadenoson or benodenoson) is recommended. This constitutes an adequate method to quantify the absolute MBF and calculate CFR or determine the response of MBF to cold (endothelial dysfunction). (61)	IIb	C
SPECT is not recommended due to its low sensitivity	III	B
Cardiac magnetic resonance is indicated in all patients with MINOCA without a clear underlying cause. (4,6,47,50,52)	I	B
Non-invasive CCTA can elucidate hidden causes of MINOCA in conventional CA (SCAD, occult occlusions) and non-invasively assess FFR. (50,51,62).	IIb	B

4.3.4 Cardiomyopathies

Occasionally, cardiomyopathies present as MINOCA, including dilated cardiomyopathy and hypertrophic cardiomyopathy. (52) Cardiac magnetic resonance would contribute to the differential diagnosis of these entities, mainly through morphological evaluation and the presence of LGE.

5. SPONTANEOUS CORONARY THROMBOSIS IN MINOCA

Acute coronary artery thrombosis can be associated with plaque accident (rupture, erosion, ulceration, calcium nodule), but it can also occur without evidence of underlying atherosclerotic disease; as we will develop in this section. In both cases, intracoronary thrombosis can be related to hypercoagulable conditions (hereditary or acquired), which should be suspected and studied, since they may have specific treatment (Table 4).

5.1 Thrombophilias and arterial thrombosis

Thrombophilias are congenital or acquired abnormalities that predispose to the onset of arterial and venous thrombotic events.

Hereditary thrombophilias are not uncommon in the general population and are found in 14% of patients with MINOCA. (6) They are more frequent in young women and vary according to race and ethnicity. (63) Examples include factor V Leiden, elevated Von Willebrand factor, protein C or protein S resistance or deficiency, and plasminogen activator inhibitor (PAI) polymorphism. (64) The latter has proved to increase the risk of coronary artery disease, especially the homozygous 4G4G variant (the heterozygous variant is common in the general population). The rest of the hereditary thrombophilias are mostly associated with venous events; hence, they should not be studied in arterial phenomena such as MINOCA. (65)

Patients with acquired thrombophilias have a higher prevalence of myocardial infarction (and other arterial or venous thromboses) than the general population; the clinical entity with the greatest physiopathogenic weight is the antiphospholipid syndrome. Thrombotic thrombocytopenic purpura (TTP), onco-hematological diseases and paroxysmal nocturnal hemoglobinuria also belong to this group, although with a lower prevalence. Exposure to heparin should lead to consider the presence of heparin-induced thrombocytopenia.

Since the COVID-19 pandemic, new knowledge is being gained about the prothrombotic effects of coronavirus infection and vaccine-induced thrombotic thrombocytopenia (VITT) on the prevalence and evolution of cardiovascular events. (66,67) However, robust conclusions cannot yet be drawn to comment on these findings. (68)

Table 4. Suspicion of hypercoagulable disorders

Suspect the presence of acquired or hereditary hypercoagulable disorders in patients with MINOCA with the following characteristics:
- Young patients, especially women without risk factors.
- Anemia, thrombocytopenia and schistocytes in blood smear (TTP).
- Previous thrombosis, pregnancy complications, stroke, low platelet count or increased KPTT (antiphospholipid syndrome).).
- Previous venous or arterial thromboses (onco-hematological).
- Exposure to heparin and decrease in platelet count (>50% compared to the value before heparin use [heparin-induced thrombocytopenia (HIT)].
- COVID infection or recent vaccination with suspected VITT drugs.

5.2 Treatment (Table 5)

In the case of suspected or proven IC thrombosis, it is reasonable to continue with double antiplatelet therapy for at least one month or until the diagnosis of thrombophilia is completed. Aspirin treatment must remain indefinitely.

Anticoagulant treatment with vitamin K antagonists is indicated only in patients with antiphospholipid syndrome, in addition to aspirin (INR between 2 and 3). Treatment with direct oral anticoagulants (DOAC) is not indicated. (69)

Table 5. Recommendations for the performance of studies and treatment in patients with suspected or confirmed hypercoagulable disorders

Recommendation	Class	Level of evidence
In case a hypercoagulable state is suspected, refer the patient to a hematology specialist for study and indication of anticoagulant and other specific treatment, when appropriate.	I	C
The study of procoagulant factors should be performed at least 12 weeks after the acute event and should include at least the 3 tests associated with the antiphospholipid syndrome and PAI polymorphism. (70)	I	B
In patients with suspected spontaneous coronary thrombosis, DAPT (ASA+P2Y12 inhibitors) should be indicated, from the acute phase until completing the thrombophilic studies	IIa	C
In patients with antiphospholipid syndrome, anticoagulation with vitamin K antagonists should be initiated. (69)	I	B
The use of DOAC is not indicated (69)	III	B

6. TREATMENT OF MINOCA

The treatment of MINOCA will depend on the underlying disease producing it. The importance of using algorithms to establish the cause is essential. In cases where the etiology of MINOCA has not been confirmed, the concept of clinical suspicion (arteries with atherosclerotic disease, COVADIS criteria for epicardial artery spasm and microvascular disease) plays an important role for empirical treatment.

6.1 Treatment of specific causes (Table 6)

6.1.1 Atherosclerotic infarction

Given that a high percentage of MINOCA cases have the same pathophysiology as ACS with significant obstructive disease, strict and monitored measures to control coronary risk factors (smoking, hypertension, dyslipidemia and diabetes) are reasonable to consider and of fundamental importance, as well as the stimulus to promote physical activity, weight control and a healthy diet, as established by the consensus on cardiovascular prevention of the Argentine Society of Cardiology. (71)

Regarding pharmacological treatment, one of the most internationally recommended drugs in MINOCA is aspirin, especially when there is evidence or high suspicion of PE or PR. (1,2,72-74)

Dual antiplatelet therapy is the treatment of choice in ACS. (75,76) On the other hand, the evidence in MINOCA is contradictory, limited, biased and comes from retrospective multicenter European registry analyses (SWEDEHEART, Pro ACS) or from post hoc subgroup analyses of randomized studies with populations such as that of the CURRENT-OASIS 7 study, where the use of DAPT in 1599 patients with MINOCA showed that even with high doses of clopidogrel the risk of major cardiovascular events increased without an increase in bleeding (HR 2.74; p=0.033) (77-79).

The Swedish registry SWEDEHEART (77) performed a 4-year evolution analysis in 9136 patients with a diagnosis of infarction without coronary obstructions >50%. The use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) demonstrated an 18% reduction in major cardiovascular events (HR 0.82; 95% CI 0.73-0.93), and the use of statins a decrease of 23% (HR 0.77; 95% CI 0.68-0.87). A reduction of major cardiovascular events was found with beta-blockers, but without reaching a statistically significant difference (14% decrease; HR 0.86; 95% CI 0.74-1.01, p=ns), and with DAPT there were no significant differences for the composite endpoint at 1 year (HR 0.90; 95% CI 0.74-1.08).

In all cases, the use of DAPT should be carefully evaluated given the risk-benefit equation: ischemic risk vs. bleeding risk.

In 2021, Nordenskjöld et al. presented the MINOCA-BAT study (79), a multicenter, prospective, randomized, controlled and open-label study that will attempt to evaluate in a 2 x 2 factorial design the usefulness of beta-blockers and ACEI/ARBs to reduce the composite endpoint of all-cause mortality, infarction readmission, stroke, or heart failure in the follow-up of patients without left ventricular dysfunction or heart failure during hospitalization.

6.1.2 Infarction of non-atherosclerotic causes

6.1.2.1 Vasospastic angina

In vasospastic angina, suspension of tobacco use and maintenance of adequate control of blood pressure, glycemia, lipids and body weight should be recommended. (37)

Nitrates are the drugs of choice and calcium blockers, alone or in combination with nitrates, are used in cases of refractory episodes to monotherapy. An average dose of 240-360 mg/day of verapamil or diltiazem, or 40-60 mg day of nifedipine, prevents 90% of coronary spasm.

Beta-blockers are not recommended in this type of angina, because by blocking the beta-effect the alpha-vasoconstrictor effect can be released. (80)

6.1.2.2 Microvascular angina

Microvascular angina has different mechanisms. The BHF CorMicA study (British Heart Foundation Coronary Microvascular Angina) study (45), analyzed in a population of patients with ischemia and non-obstructive coronary artery disease (INOCA), whether a treatment stratified according to the coronary physiology studied invasively improves the quality of life vs. standard treatment. The population with microvascular disorder was treated with beta-blockers (nebivolol), changes in lifestyle, statins and ACEI, and patients with vasospastic angina were treated by encouraging smoking cessation and lifestyle changes, together with use of calcium blockers and long-acting nitrates. The response at 6 months was a significant reduction in anginal events and a significant increase in quality of life, which suggests that the invasive evaluation of coronary physiology and the pathophysiological understanding of symptoms allow personalized treatment (precision medicine) with improved quality of life.

The REACH registry (81) found no benefits in the prolonged use of beta-blockers, both in patients with previous infarction as in patients with coronary artery disease without previous infarction and patients with cardiovascular risk factors. Statins could have a protective mechanism through their action on the endothelium. Calcium blockers present an erratic response. In some studies, they have shown benefit, probably due to the mixed behavior of vasoconstriction at microvascular level. Nitrates, despite being of some use at the moment of angina, are usually poorly tolerated in these patients.

Angiotensin-converting enzyme inhibitors/ARBs deserve a special mention. Studies from the 1990s, such as the one by Kaski et al. (82), showed the beneficial effects of these drugs by reducing events in patients recognized at that time as syndrome X. The mechanism is not entirely clear. One of the hypotheses would be that these drugs could improve microvascular function by counteracting the vasoconstrictor effect of angiotensin II.

Regardless of treatment duration, and although not determined on the basis of data from randomized studies, some registries show a tendency to symptom reduction after 6 months of the event, so it would be prudent to maintain treatment and reevaluate it upon completion of that period, according to each case.

6.1.2.3 Coronary artery dissection

Once the diagnosis of SCAD has been made, conservative treatment should be preferred (based on expert opinion). (83-86) Routine recurrent coronary angiography should be avoided at follow-up, since the benefit does not outweigh the potential risks (iatrogenic dissections). Extracoronary arterial imaging studies are recommended given the association with fibromuscular dysplasias in other territories.

There are no guidelines regarding the optimal medical management of SCAD. There is favorable evidence for the use of beta-blockers. (84)

6.1.3 Second-line or elective antianginal therapies

Trimetazidine, ranolazine (both available in the country), and nicorandil (not available in the country) are drugs with less evidence on hard endpoints in MINOCA (87-91). The meta-analysis by Zhu et al. has reported that ranolazine and nicorandil could have beneficial effects on myocardial perfusion reserve index and microvascular resistance index in patients with MVD. (92) In any case, they constitute alternatives that could be indicated in steps, in refractory cases to the aforementioned first-line medications. The evidence is even less firm in the case of other drugs such as aminophylline or dipyridamole, explored with little evidence in stable coronary conditions and minimal in MINOCA.

Table 6. Treatment of MINOCA (thrombosis in a specific section)

Recommendation	Class	Level of evidence
Suspicion or evidence of PR or PE: start with antiplatelet drugs, according to the national guidelines for ACS. (75,76)	I	C
Intensive-dose statins in all patients with MINOCA. (77)	I	B
In cases of evidence or high suspicion of epicardial coronary artery vasospasm or microvascular spasm, the use of calcium blockers (diltiazem, verapamil) and nitrates (intravenous and oral) is recommended. (93-97)	I	B
In cases of evidence or high suspicion of MVD, the use of beta-blockers (nebivolol), calcium blockers, statins, and ACEI and ARBs is recommended, except for contraindications or intolerance.	IIa	C
In patients with microvascular dysfunction not responding to the above recommendations, treatment with trimetazidine or ranolazine is recommended.	IIa	C
In cases of SCAD, beta-blockers along with aspirin are recommended.	IIa	C

MINOCA: Myocardial infarction with non obstructive coronary arteries. ACEI: Angiotensin converting enzyme inhibitors. ARBs: Angiotensin II receptor blockers

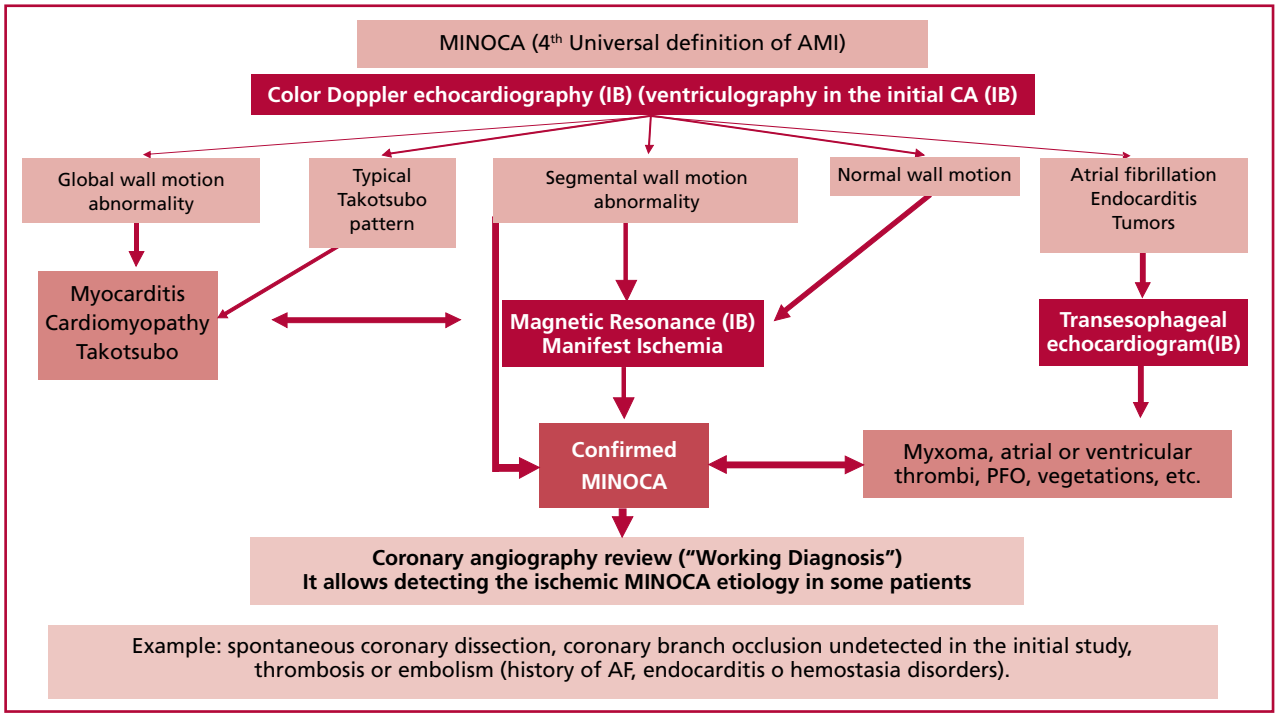

Fig. 1. Algorithm for the diagnosis of MINOCA

MINOCA: Myocardial infarction with non obstructive coronary arteries. AMI: Acute myocardial infarction. CA: Coronary angiography. PFO: Patent foramen ovale.

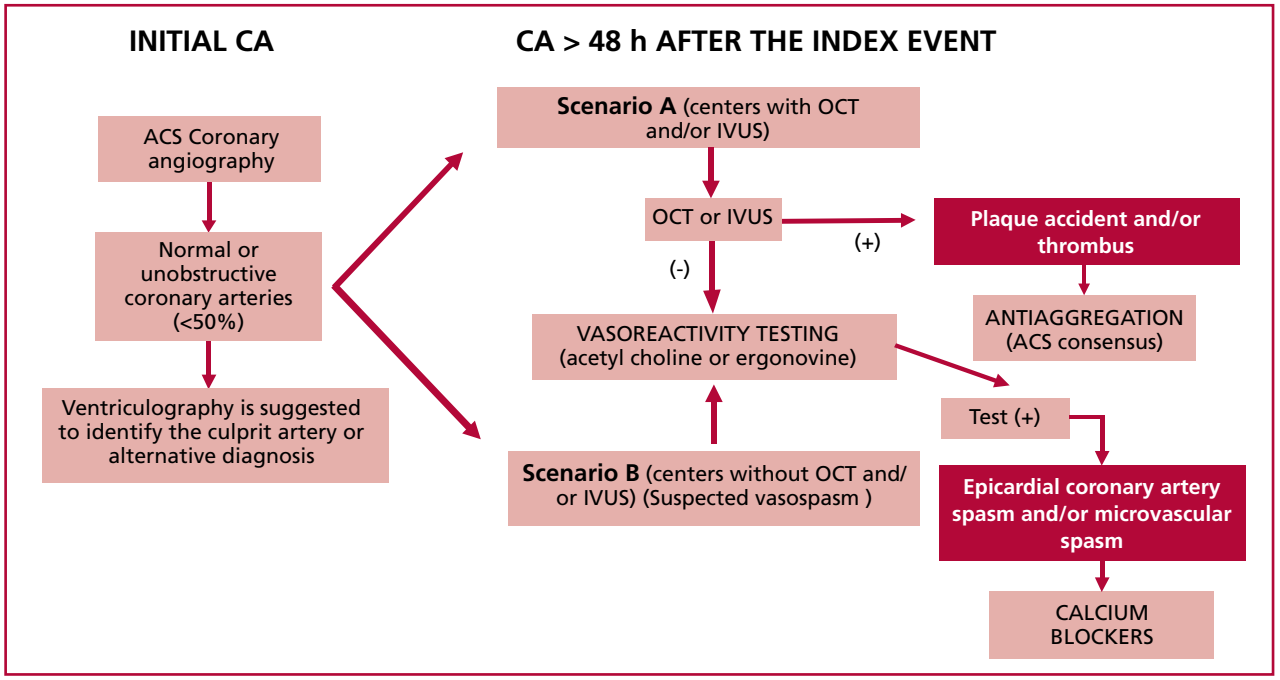

Fig. 2. Diagnosis of the cause of MINOCA according to center possibilities

Scenario A: Center with OCT/IVUS possibility
Scenario B: Center without possibility of performing intracoronary imaging studies

CA: Coronary angiography. ACS: Acute coronary syndrome. OCT: Optical coherence tomography. IVUS: Intravascular ultrasound
MINOCA: Myocardial infarction with non obstructive coronary arteries

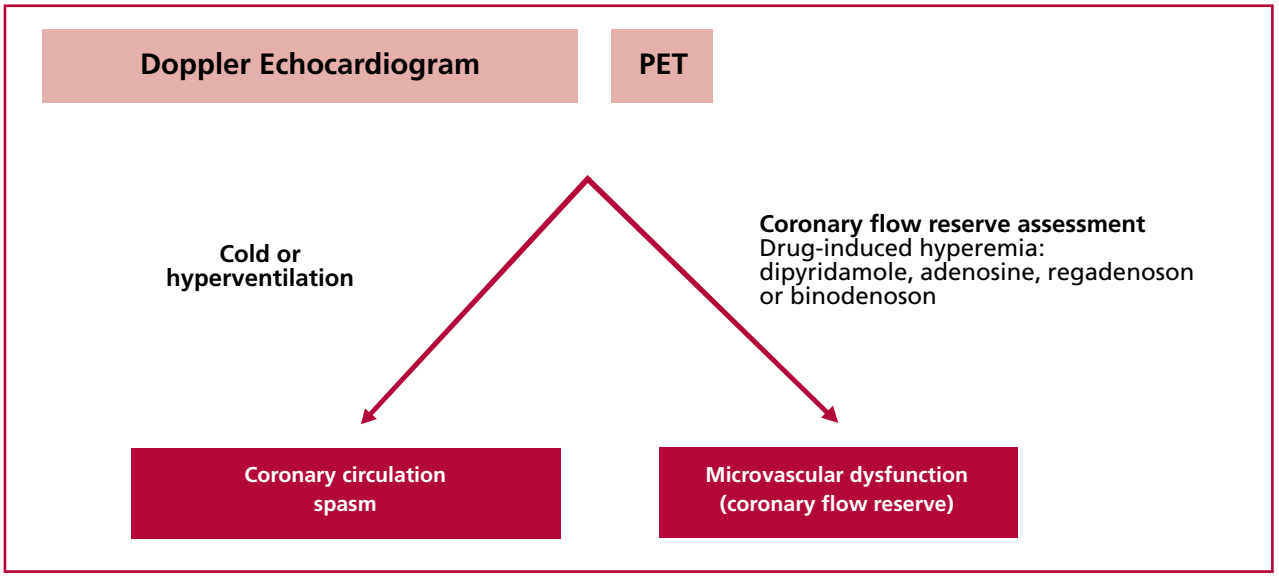

Fig. 3. Algorithm for the diagnosis of MINOCA

Coronary circulation spasm or coronary flow reserve assessment

PET: Positron-emission tomography

7. FUTURE PERSPECTIVES

The definition of MINOCA as a syndrome has enabled to encompass a series of acute coronary diseases of ischemic origin that cannot be explained by the classic coronary obstruction of atherosclerotic cause. The simplicity and complexity of this pathology lies in following the diagnostic algorithms, in order to determine the underlying cause that produces it. There is no doubt that the development of imaging techniques has been able to consolidate the diagnosis of this pathology. At present, in medicine in general and particularly in cardiology, diagnostic imaging constitutes the new paradigm. Today, CMR and OCT allow confirming the diagnosis of patients with MINOCA and differentiate them from diseases specific of the myocardium. By performing IC imaging studies, the etiology of AMI can be established and the correct treatment adopted.

In the future, these tools should be used systematically to determine the etiology of MINOCA. Undoubtedly, with time, these techniques will improve and make the diagnosis even easier.

This consensus is the cornerstone for the adequate future study of patients with MINOCA in health centers and systems of our country that incorporate the appropriate algorithms and highly complex technologies, and also for the creation of reference centers specialized in this issue. Moreover, the need to perform vasoreactivity tests in the catheterization lab and the availability of drugs such as ACh should also be emphasized.

Finally, there is need to increase the evidence with randomized studies to provide scientific support to the treatments, according to the etiology causing MINOCA.

Coronary microcirculation constitutes a very complex chapter of coronary disease, which must be studied thoroughly and systematically to better understand its pathophysiology, diagnosis, and therapy.

8. LIMITATIONS

At present, many limitations can be observed in this consensus, both in terms of recommendations as in the real possibilities of carrying out the studies that are proposed. However, this situation does not only occur in our country, but also in developed countries, given that only in recent years the term MINOCA has been incorporated in a systematic way. Nevertheless, we have made a great effort and have a strong commitment to advance algorithms and recommendations that, undoubtedly, can and should be improved for the reasons already explained. Moreover, we have considered the deficit of highly complex equipment and we gave priority to the Argentine reality, assembling two assessment scenarios to the detriment of the ideal for the possible.

9. CONCLUSIONS

MINOCA (infarction without obstructive coronary disease with stenosis <50%) is an AMI with around 6% prevalence. This entity is more frequent in young, female patients compared with infarctions with atheroscle-

rotic obstructive coronary disease. This AMI category has been incorporated into the 4th universal definition of infarction. It is a clinical-angiographic syndrome, since the diagnosis requires sine qua non a coronary angiography and determining the ischemic cause. High troponin levels do not indicate the ischemic cause and can increase due to myocardial inflammation (myocarditis) or extracardiac causes, such as pulmonary embolism; therefore, CMR imaging is a fundamental tool when the underlying cause is not evident. The origin of coronary ischemia requires a diagnostic process, "working diagnosis", in which the angiography is reevaluated, looking for spontaneous coronary dissection or total obstruction of coronary branches that went unnoticed in a first instance. It may also require intracoronary studies (OCT/IVUS) to know whether it is of atherothrombotic origin, due to in situ thrombi or cardioembolism. In the case of normal coronary arteries or absence of thrombus, demonstration of epicardial or microcirculatory coronary spasm will require invasive or non-invasive vasoreactivity testing. Similarly, microcirculatory evaluation with endothelium-independent (adenosine) or endothelium-dependent (ACh or cold test) hyperemia testing can provide additional data, which can help to choose the correct therapy.

Treatment should be directed to the cause that originated MINOCA. If there is an atherothrombotic cause, antiplatelet therapy is used according to the corresponding guidelines. Statins appear to improve the outcome and are routinely recommended. In the event that calcium antagonists is diagnosed, calcium antagonists are the drugs of choice. Angiotensin converting enzyme inhibitors/ARBs and beta-blockers (nebivolol) are recommended in patients with coronary microcirculation dysfunction. Conservative treatment is suggested in patients with SCAD. In patients with prothrombotic risk factors, antiplatelet or anticoagulation drugs are indicated.

REFERENCES

1. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017;38:143-153.
2. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation 2019;139:e891-e908.
3. Pustjens TFS, Appelman Y, Damman P, Ten Berg JM, Jukema JW, de Winter RJ et al. Guidelines for the management of myocardial infarction/injury with non-obstructive coronary arteries (MINOCA): a position paper from the Dutch ACS working group. Neth Heart J 2020;28:116-130.
4. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72:2231-2264.
5. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897-902.
6. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861-70.
7. Gerbaud E, Arabucki F, Nivet H, Barbey C, Cetran L, Chassaing S et al. OCT and CMR for the Diagnosis of Patients Presenting With MINOCA and Suspected Epicardial Causes. JACC Cardiovasc Imaging 2020;13:2619-2631.
8. Reynolds HR, Maehara A, Kwong RY, Sedlak T, Saw J, Smilowitz NR et al. Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women. Circulation 2021;143:624-640.
9. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Camma G et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. Eur Heart J 2018;39:91-98.
10. Kang WY, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ et al. Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? Int J Cardiol 2011;146:207-12.
11. Grodzinsky A, Arnold SV, Gosch K, Spertus JA, Foody JM, Beltrame J et al. Angina Frequency After Acute Myocardial Infarction In Patients Without Obstructive Coronary Artery Disease. Eur Heart J Qual Care Clin Outcomes 2015;1:92-99.
12. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J 2013;34:719-28.
13. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol 2013;62:1748-58.
14. Ijichi T, Nakazawa G, Torii S, Nakano M, Yoshikawa A, Morino Y et al. Evaluation of coronary arterial calcification - Ex-vivo assessment by optical frequency domain imaging. Atherosclerosis 2015;243:242-7.
15. Kramer MC, Rittersma SZ, de Winter RJ, Ladich ER, Fowler DR, Liang YH et al. Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. J Am Coll Cardiol 2010;55:122-32.
16. Cao M, Zhao L, Ren X, Wu T, Yang G, Du Z et al. Pancoronary Plaque Characteristics in STEMI Caused by Culprit Plaque Erosion Vs. Rupture: 3-Vessel OCT Study. JACC Cardiovasc Imaging 2021;14:1235-1245.
17. Saw J, Mancini GBJ, Humphries KH. Contemporary Review on Spontaneous Coronary Artery Dissection. J Am Coll Cardiol 2016;68:297-312.
18. Saw J, Aymong E, Mancini GB, Sedlak T, Starovoytov A, Ricci D. Nonatherosclerotic coronary artery disease in young women. Can J Cardiol 2014;30:814-9.
19. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M et al. Trends of Incidence, Clinical Presentation, and In-Hospital Mortality Among Women With Acute Myocardial Infarction With or Without Spontaneous Coronary Artery Dissection: A Population-Based Analysis. JACC Cardiovasc Interv 2018;11:80-90.
20. Garcia-Guimaraes M, Bastante T, Macaya F, Roura G, Sanz R, Barahona Alvarado JC et al. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. Rev Esp Cardiol (Engl Ed) 2021;74:15-23.
21. Shibata T, Kawakami S, Noguchi T, Tanaka T, Asaumi Y, Kanaya T et al. Prevalence, Clinical Features, and Prognosis of Acute Myocardial Infarction Attributable to Coronary Artery Embolism. Circulation 2015;132:241-50.
22. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565-2568.
23. Kaski JC, Crea F, Meran D, Rodriguez L, Araujo L, Chierchia S et al. Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina. Circulation 1986;74:1255-65.
24. Ciliberti G, Seshasai SRK, Ambrosio G, Kaski JC. Safety of intracoronary provocative testing for the diagnosis of coronary artery spasm. Int J Cardiol 2017;244:77-83.
25. Chen C, Wei J, AlBadri A, Zarrini P, Bairey Merz CN. Coronary Microvascular Dysfunction- Epidemiology, Pathogenesis, Prognosis, Diagnosis, Risk Factors and Therapy. Circ J 2016;81:3-11.
26. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U et al. International standardization of diagnostic criteria for microvascular angina. Int J Cardiol 2018;250:16-20.
27. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. Circulation 2017;135:1075-1092.
28. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. Cardiology 2002;97:197-202.
29. Yasue H, Horio Y, Nakamura N, Fujii H, Imoto N, Sonoda R et al. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. Circulation 1986;74:955-63.
30. Gutierrez EGL, J. Escaned, J. Cruz, I. Ojeda, S. Romaguera, R. Moreno, R. . Valoración de la función endotelial y provocación de vasoespasmo coronario mediante infusión intracoronaria de acetilcolina. Documento técnico de la ACI-SEC. REC Interv Cardiol 2021.
31. Sueda S, Miyoshi T, Sasaki Y, Sakaue T, Habara H, Kohno H. Safety and optimal protocol of provocation test for diagnosis of multivessel coronary spasm. Heart Vessels 2016;31:137-42.
32. Higuma T, Soeda T, Abe N, Yamada M, Yokoyama H, Shibutani S et al. A Combined Optical Coherence Tomography and Intravascular Ultrasound Study on Plaque Rupture, Plaque Erosion, and Calcified Nodule in Patients With ST-Segment Elevation Myocardial Infarction: Incidence, Morphologic Characteristics, and Outcomes After Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2015;8:1166-1176.
33. Duronto EANEJLB, J.; Cosntantin,, I. Consenso para el manejo de pacientes con dolor precordial. . Revista Argentina de Cardiologia 2016;84:378-401.

34. Rigo F. Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. Cardiovasc Ultrasound 2005;3:8.
35. Galiuto L, Picano E. Stress echo in microvascular disease. In: Picano E. Stress echocardiography.: Springer International Publishing.
36. Mandoli GE, Cameli M, Minardi S, Crudele F, Lunghetti S, Mondillo S. Layer-specific strain in dipyridamole stress echo: A new tool for the diagnosis of microvascular angina. Echocardiography 2018;35:2005-2013.
37. Group JCSJW. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 2014;78:2779-801.
38. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-95.
39. Shimokawa H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. Eur Heart J 2014;35:3180-93.
40. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-477.
41. Schindler TH, Bateman TM, Berman DS, Chareonthaitawee P, De Blanche LE, Dilsizian V et al. Appropriate Use Criteria for PET Myocardial Perfusion Imaging. J Nucl Med 2020;61:1221-1265.
42. Campisi R, Marengo FD. Coronary microvascular dysfunction in women with nonobstructive ischemic heart disease as assessed by positron emission tomography. Cardiovasc Diagn Ther 2017;7:196-205.
43. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R et al. Anatomic vs. physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol 2013;62:1639-1653.
44. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:2625-2641.
45. Ford TJ, Stanley B, Sidik N, Good R, Rocchiccioli P, McEntegart M et al. 1-Year Outcomes of Angina Management Guided by Invasive Coronary Function Testing (CorMicA). JACC Cardiovasc Interv 2020;13:33-45.
46. Chopard R, Jehl J, Dutheil J, Genon VD, Seronde MF, Kastler B et al. Evolution of acute coronary syndrome with normal coronary arteries and normal cardiac magnetic resonance imaging. Archives of cardiovascular diseases 2011;104:509-17.
47. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2017;19:75.
48. Dastidar AG, Rodrigues JC, Johnson TW, De Garate E, Singhal P, Baritussio A et al. Myocardial Infarction With Nonobstructed Coronary Arteries: Impact of CMR Early After Presentation. JACC Cardiovascular imaging 2017.
49. Norgaard BL, Terkelsen CJ, Mathiassen ON, Grove EL, Botker HE, Parner E et al. Coronary CT Angiographic and Flow Reserve-Guided Management of Patients With Stable Ischemic Heart Disease. Journal of the American College of Cardiology 2018;72:2123-2134.
50. Yoo SM, Jang S, Kim JA, Chun EJ. Troponin-Positive Non-Obstructive Coronary Arteries and Myocardial Infarction with Non-Obstructive Coronary Arteries: Definition, Etiologies, and Role of CT and MR Imaging. Korean journal of radiology 2020;21:1305-1316.
51. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992-2002.
52. Dastidar AG, Rodrigues JC, Ahmed N, Baritussio A, Bucciarelli-Ducci C. The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. Current cardiovascular imaging reports 2015;8:28.
53. Tornvall P, Gerbaud E, Behaghel A, Chopard R, Collste O, Laraudogoitia E et al. Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: A meta-analysis of individual patient data. Atherosclerosis 2015;241:87-91.
54. Doltra A, Stawowy P, Dietrich T, Schneeweis C, Fleck E, Kelle S. Magnetic resonance imaging of cardiovascular fibrosis and inflammation: from clinical practice to animal studies and back. BioMed research international 2013;2013:676489.
55. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. Journal of the American College of Cardiology 2018;72:3158-3176.
56. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. Journal of the American College of Cardiology 2009;53:1475-87.
57. Laraudogoitia Zaldumbide E, Perez-David E, Larena JA, Velasco del Castillo S, Rumoroso Cuevas JR, Onaindia JJ et al. The value of cardiac magnetic resonance in patients with acute coronary syndrome and normal coronary arteries. Rev Esp Cardiol 2009;62:976-83.
58. Fernandez-Perez GC, Aguilar-Arjona JA, de la Fuente GT, Samartin M, Ghioldi A, Arias JC et al. Takotsubo cardiomyopathy: assessment with cardiac MRI. AJR American journal of roentgenology 2010;195:W139-45.
59. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. European heart journal 2015;36:475-81.
60. Mitchell JH, Hadden TB, Wilson JM, Achari A, Muthupillai R, Flamm SD. Clinical features and usefulness of cardiac magnetic resonance imaging in assessing myocardial viability and prognosis in Takotsubo cardiomyopathy (transient left ventricular apical ballooning syndrome). The American journal of cardiology 2007;100:296-301.
61. Maltseva A, Mochula A, Vorobyeva D, Gulya M, Ryabov V, Zavadovsky K. The usage CZT SPECT to assess myocardial blood flow and flow reserve in myocardial infarction with non-obstructive coronary arteries patients. European Heart Journal - Cardiovascular Imaging 2021;22.
62. Gard A, Lindahl B, Batra G, Hadziosmanovic N, Hjort M, Szummer KE et al. Interphysician agreement on subclassification of myocardial infarction. Heart 2018;104:1284-1291.
63. Zakai NA, McClure LA. Racial differences in venous thromboembolism. J Thromb Haemost 2011;9:1877-82.
64. Liang Z, Jiang W, Ouyang M, Yang K. PAI-1 4G/5G polymorphism and coronary artery disease risk: a meta-analysis. Int J Clin Exp Med 2015;8:2097-107.
65. Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematology Am Soc Hematol Educ Program 2016;2016:1-9.
66. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020;324:799-801.
67. Cines DB, Bussel JB. SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med 2021;384:2254-2256.
68. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:2950-2973.
69. Sayar Z, Moll R, Isenberg D, Cohen H. Thrombotic antiphospholipid syndrome: A practical guide to diagnosis and management. Thromb Res 2021;198:213-221.
70. Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS et al. 16th International Congress on Antiphospholipid Antibodies Task Force Report on Antiphospholipid Syndrome Treatment Trends. Lupus 2020;29:1571-1593.
71. Lerman J, Bluro I, Giunta G y col. Actualización del consenso de prevención cardiovascular. Revista Argentina de Cardiologia 2016;84.

72. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA et al. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. J Am Heart Assoc 2018;7.
73. Pasupathy S, Tavella R, Beltrame JF. Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): The Past, Present, and Future Management. Circulation 2017;135:1490-1493.
74. Cohen Arazi H, Iglesias R, Duronto E, Lescano A, Campisi R, Deviggiano A et al. [Myocardial ischemia without coronary obstructions: MINOCA-INOCA. Review for decision making]. Medicina (B Aires) 2020;80:253-270.
75. Trivi M, Costabel JP, Spennatto M, Duronto E, Caccavo A, Mauro V y col. Consenso Síndrome Coronario Agudos sin Elevación del Segmento ST-2019. Rev Argent Cardiol 2020;88:1-20.
76. Tajer C, Charask A, Castillo Costa Y, Allín J, Antonietti L, Berrocal D y col. Consenso de síndrome coronario agudo con elevación ST. Actualización focalizada. Rev Argent Cardiol 2019;88:1-18.
77. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A et al. Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease. Circulation 2017;135:1481-1489.
78. Montenegro Sa F, Carvalho R, Santos L, Ruivo C, Antunes A, Belo A et al. Dual antiplatelet therapy in myocardial infarction with non-obstructive coronary artery disease - insights from a nationwide registry. Rev Port Cardiol (Engl Ed) 2020;39:679-684.
79. Nordenskjold AM, Agewall S, Atar D, Baron T, Beltrame J, Bergstrom O et al. Randomized evaluation of beta blocker and ACE-inhibitor/angiotensin receptor blocker treatment in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA-BAT): Rationale and design. Am Heart J 2021;231:96-104.
80. Mejia-Renteria H, van der Hoeven N, van de Hoef TP, Heemelaar J, Ryan N, Lerman A et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. Int J Cardiovasc Imaging 2017;33:1041-1059.
81. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S et al. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308:1340-9.
82. Kaski JC, Rosano G, Gavrielides S, Chen L. Effects of angiotensin-converting enzyme inhibition on exercise-induced angina and ST segment depression in patients with microvascular angina. J Am Coll Cardiol 1994;23:652-7.
83. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jimenez-Quevedo P et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. JACC Cardiovasc Interv 2012;5:1062-70.
84. Tweet MS, Eleid MF, Best PJ, Lennon RJ, Lerman A, Rihal CS et al. Spontaneous coronary artery dissection: revascularization vs. conservative therapy. Circ Cardiovasc Interv 2014;7:777-86.
85. Lettieri C, Zavalloni D, Rossini R, Morici N, Ettori F, Leonzi O et al. Management and Long-Term Prognosis of Spontaneous Coronary Artery Dissection. Am J Cardiol 2015;116:66-73.
86. Adlam D, Alfonso F, Maas A, Vrints C, Writing C. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. Eur Heart J 2018;39:3353-3368.
87. Santoro A, Schiano Lomoriello V, Santoro C, Muscariello R, Galderisi M. Resolution of angina pectoris and improvement of the coronary flow reserve after ranolazine treatment in a woman with isolated impaired coronary microcirculation. Case Rep Cardiol 2013;2013:343027.
88. Ahmed B, Mondragon J, Sheldon M, Clegg S. Impact of ranolazine on coronary microvascular dysfunction (MICRO) study. Cardiovasc Revasc Med 2017;18:431-435.
89. Yamabe H, Namura H, Yano T, Fujita H, Kim S, Iwahashi M et al. Effect of nicorandil on abnormal coronary flow reserve assessed by exercise 201Tl scintigraphy in patients with angina pectoris and nearly normal coronary arteriograms. Cardiovasc Drugs Ther 1995;9:755-61.
90. Koruth JS, Lala A, Pinney S, Reddy VY, Dukkipati SR. The Clinical Use of Ivabradine. J Am Coll Cardiol 2017;70:1777-1784.
91. Tagliamonte E, Cirillo T, Rigo F, Astarita C, Coppola A, Romano C et al. Ivabradine and Bisoprolol on Doppler-derived Coronary Flow Velocity Reserve in Patients with Stable Coronary Artery Disease: Beyond the Heart Rate. Adv Ther 2015;32:757-67.
92. Zhu H, Xu X, Fang X, Zheng J, Zhao Q, Chen T et al. Effects of the Antianginal Drugs Ranolazine, Nicorandil, and Ivabradine on Coronary Microvascular Function in Patients With Nonobstructive Coronary Artery Disease: A Meta-analysis of Randomized Controlled Trials. Clin Ther 2019;41:2137-2152 e12.
93. Pepine CJ, Feldman RL, Whittle J, Curry RC, Conti CR. Effect of diltiazem in patients with variant angina: a randomized double-blind trial. Am Heart J 1981;101:719-25.
94. Schroeder JS, Feldman RL, Giles TD, Friedman MJ, DeMaria AN, Kinney EL et al. Multiclinic controlled trial of diltiazem for Prinzmetal's angina. Am J Med 1982;72:227-32.
95. Ginsburg R, Lamb IH, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. Am Heart J 1982;103:44-9.
96. Rosenthal SJ, Lamb IH, Schroeder JS, Ginsburg R. Long-term efficacy of diltiazem for control of symptoms of coronary artery spasm. Circ Res 1983;52:I153-7.
97. Chahine RA, Feldman RL, Giles TD, Nicod P, Raizner AE, Weiss RJ et al. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. J Am Coll Cardiol 1993;21:1365-70.