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Consensus statement

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Myocardial infarction with non-obstructive coronary arteries and, ischemia non-obstructive coronary arteries, COMECITE recommendations

Infarto de miocardio con arterias coronarias no obstructivas e isquemia de arterias coronarias no obstructivas, recomendaciones de COMECITE

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Keywords: myocardial infarction, myocardial ischemia, non-obstructive coronary arteries, invasive and non-invasive.

Palabras clave: *infarto de miocardio, isquemia miocárdica, lesiones coronarias no obstructivas, invasivo y no invasivo.*

ABSTRACT

Myocardial infarction with non-obstructive coronary arteries (MINOCA), and ischemia with non-obstructive coronary arteries (INOCA) are controversial concepts. A non-obstructive lesion with ≤ 50% stenosis in acute coronary syndromes may have an atherosclerosis process with plaque erosion or fracture and thrombus formation, which are time-dependent and not easily shown by intravascular imaging methods. The largest MINOCA Registry is the Swedish, which included 9,092 patients with MINOCA, supported only by coronary angiography without intravascular imaging, led to unknown dissection, erosion, or fracture, and did not discriminate Takotsubo, myocarditis, or cardiomyopathies. MINOCA must have positive cardiac markers or enzymes, electrocardiographic (ECG) changes, regional wall motion abnormalities (WMA), coronary angiography, and intravascular image to confirm the diagnosis. In INOCA a positive ischemic stress test, coronary angiography, and coronary hyperemic physiologic studies as fractional flow reserve (FFR), and coronary flow reserve (CFR) should be present to confirm the diagnosis.

RESUMEN

El infarto y la isquemia del miocardio sin lesiones coronarias obstructivas (MINOCA, INOCA, por sus siglas en inglés) son conceptos controvertidos. Una lesión no obstructiva ≤ 50% implica la presencia de aterosclerosis que puede complicarse con ruptura o erosión de placa y trombosis presentes en los síndromes coronarios agudos, los cuales son tiempo dependientes y no fácilmente detectables por imagen intravascular. El mayor registro de MINOCA es el sueco, que reportó 9,092 pacientes utilizando angiografía coronaria únicamente, sin imagen intravascular, lo que deja poco claro si hubo disección, erosión o ruptura de placa; así como tampoco especifica la presencia de enfermedad de Takotsubo, miocarditis o cardiomiopatía. El diagnóstico de MINOCA debe tener elevación de marcadores o enzimas cardiacas, con o sin cambios electrocardiográficos y anomalías en la movilidad segmentaria, angiografía coronaria e imagen intravascular. INOCA debe tener un estudio inductor de isquemia positivo, angiografía coronaria, estudio fisiológico coronario hiperémico con la determinación del flujo de reserva fraccional (FFR, por sus siglas en inglés) y el flujo de reserva coronaria (CFR, por sus siglas en inglés) para el diagnóstico de certeza.

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INTRODUCTION

The Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE for the name in Spanish: Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular) formed the consensus group with a designated chairman and co-chairman; that later distributed functions to the rest of the members. Every member searched and analyzed relevant publications about MINOCA and INOCA disease. The authors used the Cochrane Handbook[1] for systematic reviews of interventions and A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2): a critical appraisal tool for systematic reviews that included randomized or non-randomized study trials of healthcare interventions.[2] The members also reviewed single papers on special anatomical conditions. The consensus group discussed each paper in an expert panel format, nominal group, and anonymous Dolphy survey.[3] The consensus timing process took from October 13, 2022, to February 28, 2023. The authorship for publication follows the International Committee of Medical Journal Editors (ICMJE).[4]

MINOCA

Cardiac event characterized by clinical symptoms of an ischemic episode with chest pain or equivalent, lasting more than 10 minutes, elevated cardiac enzymes or markers, with or without electrocardiographic ST depression or elevation (type 2 myocardial infarction); non-obstructive disease (luminal stenosis < 50%) or dissection on coronary angiography and without evidence of plaque rupture or erosion with intravascular ultrasound (IVUS) or optical coherence tomography (OCT).[5]

INOCA

Myocardial ischemia acute or chronic with or without symptoms, with positive ischemic exercise or pharmacological stress test, non-obstructive coronary artery disease in coronary angiography (< 50% stenosis), and coronary hyperemic physiologic study with normal FFR, and abnormal CFR and index of microvascular resistance (IMR).[6]

CLINICAL FEATURES

Chest pain is cardinal, but other symptoms may be present in MINOCA and INOCA. The incidence of MINOCA with Non-ST segment elevation myocardial infarction (NSTEMI) is about 8-10%, while ST-Segment Elevation Myocardial Infarction (STEMI) is 2.8-4.4%. Patients with MINOCA tend to be younger, and less likely to have risk factors such as hyperlipidemia, hypertension, diabetes, and smoking. The male-female ratio for MINOCA is 2.5:1 compared with 4:1 for atherosclerotic disease.[7] Symptoms and signs of INOCA are often misdiagnosed in young and middle-aged women and men because they do not present typical anginal symptoms; the prevalence is 13-39%, patients are younger, female, and had fewer atherosclerosis risk factors,[8] which is also associated with impaired quality of life, higher disability, morbidity, mortality, and higher number of hospital readmission and repeat coronary angiographies.[6,9]

NON-INVASIVE DIAGNOSTIC APPROACH FOR MINOCA AND INOCA

Electrocardiogram (ECG)

STEMI criteria

1. S-T segment elevation straight or convex upward, blends with T to form a dome in two contiguous leads with 1.0 mV = 10 mm standardization.
2. Wide upright T or inverted T.
3. ST-segment elevation or T wave may approximate or exceed QRS height.
4. 1 mm in all standard leads other than V2 and V3.
5. 2.5 mm in leads V2 and V3 in men younger than age 40, 2 mm in leads V2 and V3 in men aged 40 and older, and 1.5 mm in these leads in women.
6. Concomitant T-wave abnormalities (wide, ample, or inverted T-waves).
7. Q waves.

8. ST depression in the reciprocal leads.
9. New left bundle branch block (LBBB).[10]

Non-STEMI criteria

1. Absence of persistent ST-segment elevation
2. ST-depression
3. Transient ST-segment elevation
4. T-wave changes[11]
5. Normal ECG

CARDIAC MARKERS AND ENZYMES

Two types of cardiac troponin (cTn) I and T are proven as biomarkers for myocardial damage. The Baseline concentration depends on the diagnostic system and varies in men, women, and age. In myocardial infarction (MI), cTn concentration peaks at 10-20 hours after occluded coronary arteries reperfusion and 24-50 hours in vessels without reperfusion. cTnI is released in a single peak, while cTnT exhibits biphasic kinetics; the first peak concurs with cTnI, and the second peak occurs after 80 hours of the first ischemic episode without reperfusion. Troponin remained increased up to 10-14 days after MI.

Other pathologies that increase cTn include heart failure, atrial fibrillation, pulmonary embolism, endocarditis, myocarditis, cardiac trauma, stable coronary artery disease, cardiotoxic agents, drugs of abuse, carbon dioxide, and venoms of spiders, scorpions, snakes, or jellyfish, stroke or brain trauma, physical exercise, skeletal muscle disorders, sepsis, SARS-CoV-2 infection or renal failure.[12]

Creatine kinase (CK) and CK subfraction MB should be performed in myocardial infarction. Their peak levels were lowest in patients with MINOCA as compared to acute coronary syndromes (ACS) with a single vessel or multivessel disease.[13]

D-dimer in ACS has prognostic value, and levels were an independent predictor of unfavorable outcomes.[14] N-Terminal Pro-B-type Natriuretic Peptide (NT-proBNP) is also an independent biomarker and is a powerful determinant of short-term cardiac risk in ACS,[15] both markers would be especially useful in the acute myocardial setting.

ECHOCARDIOGRAPHY

The technique is essential for patient assessment with myocardial infarction, chronic or acute cardiac ischemic, myocarditis, cardiomyopathy, and Takotsubo setting. CFR with adenosine or dipyridamole could be evaluated.[16,17]

Findings

1. Wall motion abnormalities with absence or reduction of systolic thickening.
2. Decreased motion score:
   a. Hypokinetic
   b. Akinetic
   c. Dyskinetic (systolic bulging)
   d. Aneurysmal
3. Compensatory hyperkinesis of non-ischemic wall.
4. Global longitudinal strain (GLS) segment abnormalities.
5. GLS Post-systolic shortening.
6. Tissue synchrony imaging abnormalities.
7. Diastolic dysfunction.
8. Mechanical complications (thrombus, right ventricular infarction, acute mitral insufficiency, septal defects, free wall rupture or pericardial effusion, and tamponade).[18-20]

Brachial flow-mediated dilation (FMD) is a useful non-pharmacological tool for endothelial function evaluation. It is positively associated with future cardiovascular events[21] and could be a surrogate marker of microvascular dysfunction.

CARDIAC COMPUTED TOMOGRAPHY SCAN (CCTs)

CCTs assess coronary, aortic, and pulmonary arteries, atrial, ventricles, and valvular anatomy, and myocardial perfusion.[22] Fractional flow reserve (CT-FFR) was recently added to the CCTs evaluation. Multidetector computed tomography has excellent accuracy (95%) in dual-energy/spectral analysis in acute myocarditis compared to cardiac magnetic resonance.[23]

CARDIAC MAGNETIC RESONANCE IMAGING (CMR)

CMR supplies reliable diagnostic information in pulmonary and aortic vessels and identifies myocardial ischemic damage versus inflammation. In MINOCA setting supplies reliable size and location information on myocardial infarction and tissue viability. CFR is determined from coronary sinus (CS) flow measurements, assuming that coronary circulation extends from the major epicardial arteries through pre-arterioles, arterioles, and capillaries draining in CS.[24]

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) AND POSITRON EMISSION TOMOGRAPHY (PET)

Both technologies evaluate cardiac perfusion and viability and supply valuable information and prognosis of coronary artery disease. SPECT with technetium-99m labeled tracer and PET with rubidium-82, N-13 ammonia, O-18 water, or F-18 flurpiridanz which is more accurate in terms of myocardial blood flow. This method does not measure blood flow in epicardial coronary arteries and CFR is not allowed. Fluorodeoxyglucose is able to assess myocarditis.[10]

Recommendations

1. Echo, PET, CCTs, or CMR should be performed before patient discharge to confirm MINOCA *(Figure 1)*.
2. In INOCA, the positive ischemic stress test should include CFR determination by echo or CMR and FMD test performed before invasive coronary angiography.

INVASIVE DIAGNOSTIC APPROACH OF MINOCA AND INOCA.

MINOCA

Urgent coronary angiography must be performed if clinical symptoms, ECG changes, cardiac markers or enzymes, and WMA are positive for the diagnosis of myocardial infarction. If no significant obstructive coronary lesion is found, an intravascular image test (IVUS or OCT) will be performed on the proper infarct artery or on multivessel where the culprit lesion has been difficult to determine. Atherosclerotic findings with plaque erosion, plaque fracture; calcified nodule; spontaneous coronary artery dissection (SCAD), or coronary artery spasm (CAS) should not be considered MINOCA[25] nor should Takotsubo syndrome, myocarditis,

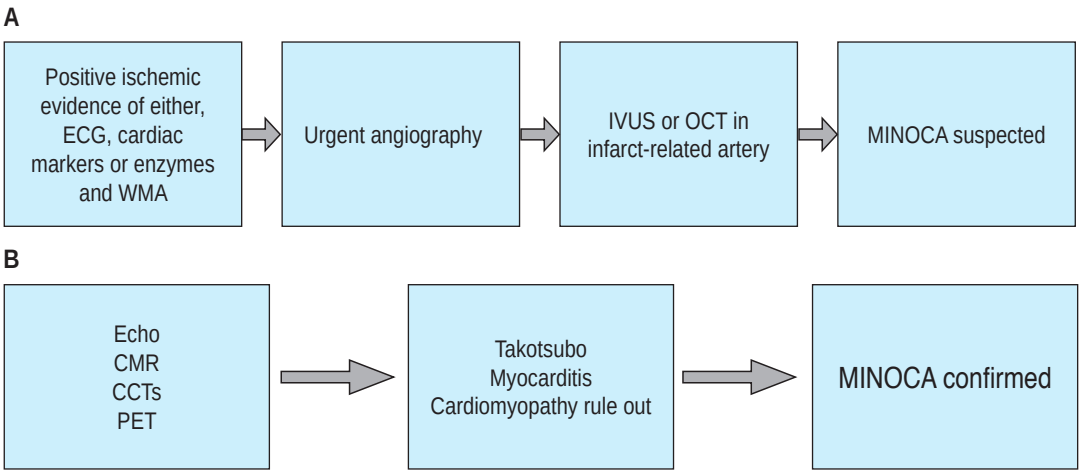

Figure 1: A) MINOCA evaluation. **B)** Predischarge evaluation.
ECG = electrocardiogram. WMA = Wall Motion Abnormalities. IVUS = intravascular ultrasound. OCT = Optical Coherence Tomography. CMR = cardiac magnetic resonance. CCTs = cardiac computed tomography scan.

or cardiomyopathies. Non-invasive studies are needed to confirm the MINOCA diagnosis before patient discharge[26] *(Figure 1)*.

INOCA

Cardiac catheterization and coronary angiography rule out non-obstructive coronary lesions. Then coronary physiology evaluation is performed with hyperemic FFR, CFR, and IMR on the related ischemic territory artery *(Figure 2)*. There be four scenarios:

1. FFR ≤ 0.80 and CFR > 2.0, the diagnosis would be flow-limiting stenosis with preserved microvascular function, and percutaneous coronary intervention (PCI) is indicated.
2. FFR ≤ 0.80 and CFR < 2.0, the diagnosis would be flow-limiting stenosis and Microvascular Dysfunction (MVD), PCI, and medical treatment is indicated.
3. FFR > 0.80 and CFR > 2.0, the diagnosis would be non-flow-limiting stenosis with preserved microvascular function, consider alternative diagnosis plus medical treatment.
4. FFR > 0.80 and CFR < 2.0, the diagnosis would be non-flow-limiting stenosis with microvascular dysfunction. Medical treatment is indicated.[27]

IMR is a microvascular evaluation index whose normal value is < 25 and would be used when CRF is < 2.0 to confirm microvascular angina. CAS with ergonovine provocation test is reserved for non-flow-limiting stenosis diagnosis with preserved microvascular function.[28]

The acetylcholine test is unavailable in Mexico and precludes its use.

Recommendations

1. IVUS or OCT must be performed in MINOCA searching atherosclerotic or calcified complicated lesions as well as SCAD and CAS.
2. Whole cardiac-cycle pressure-wire base adenosine coronary hyperemic physiologic tests such as FFR and CFR must be performed to get specific diagnoses and treatment in INOCA.
3. IMR is a microvascular evaluation index to find microvascular dysfunction.
4. Ergonovine provocation test is reserved for non-flow-limiting stenosis with preserved microvascular function diagnosis.
5. Always measured LVEDP and transaortic valve gradient.

NON-PHARMACOLOGIC TREATMENT

The 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes[29] emphasize the benefits of lifestyle changes in diet, alcohol, smoking, weight loss, physical activity, cardiac rehabilitation, psychosocial/environmental intervention, and sexual counseling as follows:

1. Vegetables 200 g or more per day.
2. Dietary fiber 35-45 g per day, especially whole grains.
3. Unsalted nuts 30 g per day.
4. Fish, especially oily fish, 1-2 servings per week.
5. Limited lean meat.
6. Low-fat dairy products.
7. Liquid vegetable oils.
8. Saturated fats < 10% of total energy intake.
9. Replace saturated with polyunsaturated oils.

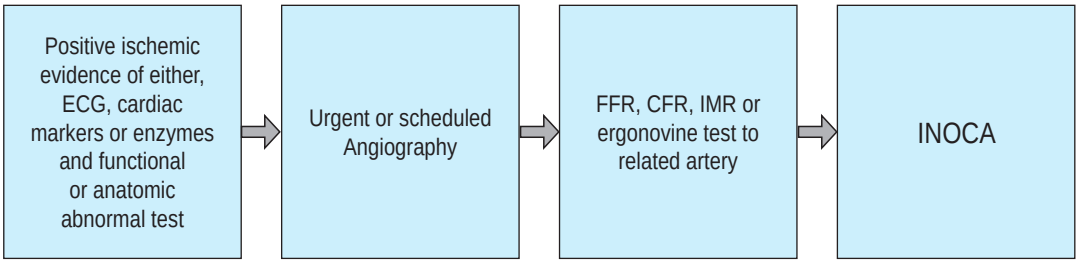

Figure 2: INOCA evaluation.
ECG = electrocardiogram. FFR = fractional flow reserve. CFR = coronary flow reserve. IMR = index of microvascular resistance.

10. Avoid trans-unsaturated fats.
11. Avoiding preprocessed food.
12. Consume ≤ 5-6 g of salt per day.
13. Limit alcohol to ≤ 100 g/week, or < 15 g/day, consider cero alcohol intake.
14. Avoid high-sugar food, especially soft drinks.
15. Quit smoking, considering nicotine replacement, e-cigarette, bupropion, and varenicline.
16. Reduce and/or keep body mass index, to < 25 kg/m^2.
17. Encourage moderate aerobic activity 30-60 min/day, for at least five days/week.
18. Promote exercise-based cardiac rehabilitation.
19. Recognize mental disorders and treat them with psychological and/or pharmacological interventions.
20. Reduce exposure to pollution by limiting polluted air and excessive noise.
21. Recommend air purifiers and face masks.
22. Sexual activity is usually safe.
23. Pharmacological treatment for erectile dysfunction is usually safe.

These recommendations may work with or without significant epicardial coronary stenosis, as they may improve endothelial integrity, plaque stability, and microvascular dysfunction under certain conditions.

Diet

There is experimental evidence that obesity and high fat, high sugar, and low fiber diet (Western diet) may cause unhealthy gut microbiota, higher body weight, and body fat percentage, and endothelial dysfunction due to a reduction in nitric oxide synthase following the increased release of adipose tissue release of interleukin, interferon and, tumor necrosis factor from adipose tissue.[30,31]

Current knowledge provides solid evidence of the interaction between all the non-pharmacological interventions, especially diet, with dysbiosis of the gut microbiota and eubiotics, through various metabolites that act pro and against endothelial hemostasis. The article of Jessica Maiuolo et al. supplies a clear and simplified overview of these concepts, particularly the importance of proper nutrition for healthy gut microbiota, as the benefits of taking prebiotics and probiotics.[32]

The Mediterranean diet contains healthier plant-based nutrients, including oils and whole grains, as well as natural agricultural and marine products with significant amounts of antioxidants, low processed food, simple carbohydrates, and, beef, which create a more stable gut microbiota that leads to local production of short-chain fatty acids, that cannot otherwise be supplied externally and that enter the portal circulation, resulting in improved metabolism and weight.[33] These benefits are accompanied by fewer harmful metabolites, such as trimethylamine N-oxide (TMAO), which is abundant in the Western diet.[34,35] This diet receives attention because of its known cardiovascular benefits, high amounts of nuts and olive oil, low-saturated fat, and low-meat diet, which may improve the endothelium of healthy individuals and those at cardiovascular risk, particularly endothelial function as measured by FMD. Mechanisms involved in this improvement in endothelial function include:[36,37]

- ↓ Oxidative stress, inflammation, and platelet aggregation.
- ↓ Cancer-related hormones and growth factors.
- ↓ Low-density lipoprotein.
- ↓ Inflammatory markers.
- ↓ Hyperglycemia-induced endothelial dysfunction.
- ↑ Nitric oxide bioavailability through more L-arginine.
- ↑ High-density lipoprotein.
- ↑ Eubiosis.

Vitamins (A, C, D, and E), carotenoids, polyphenols, flavonoids, selenium, iron, copper, zinc, and manganese, natural antioxidants, may regulate vascular oxidative stress and promote reendothelialization and vascular repair.[38]

Dysbiosis is also associated with overexpression of vasoconstrictor substances (endothelin, thromboxane A2, angiotensin II, etc.) and reactive oxygen species which then from superoxide anion, leading to inflammation, dysfunction, and increased permeability of the endothelium with further leukocyte infiltration and various types of

vascular catastrophes, including endothelial erosion, rupture, and thrombosis, apart from other late complications such as cancer, neurological disorders, etcetera.[39,40]

The link between microbiota health, obesity, and endothelial function is supported by recent experimental transplantation of feces from obese human donors to germ-free mice, which develop glucose intolerance and impaired endothelial function, without gaining weight compared with mice receiving feces from lean human donors. Experimental information also shows protection against atherosclerosis after feces of a healthy microbiota and microbiome transplants.[41-43]

Another important relationship of the microbiota concerns the very low calories ketogenic diet, which can provide benefits if it consists mainly of polyunsaturated oils, predominantly plant rather than animal proteins, complex rather than simple carbohydrates, abundant fiber, and avoidance of artificial sweeteners; more short chain fatty acids, improved diversity of bacteria, Achaea and Eukarya with a propensity for a healthier metabolism, including greater insulin sensitivity, weight loss, and lipid balance, leading to less oxidative stress, less chronic low-intensity inflammation, and better endothelial performance.[44,45] The pre and probiotics undoubtedly enhance these benefits.[46-48]

Sedentariness can also lead to dysbiosis in men and women, and physical activity can lead back to eubiosis.[49,50] Lifestyle conditions such as dietary habits, lack of exercise or physical activity, mental state, and physical environment correspond to the exposome, which influences the epigenetic conditions of the microbiota.[51,52]

Low concentration of ketones, specially β-hydroxybutyrate, and acetoacetate is present in hyperglycemia, during the ketogenic diet, brings several benefits to cardiovascular health, including improved insulin sensitivity and endothelial function, and eventually antioxidant, anti-inflammatory and anti-aging effects:[53-55]

↓ Weight
↓ LDL-cholesterol.
↓ Triglycerides.
↓ HbA1c.
↓ Blood glucose.
↓ Low-intensity chronic inflammation.

↓ Pathological cardiac remodeling.
↓ Mitochondrial oxidative stress.

↑ Ketonemia.
↑ Histone β-hydroxybutyrylation.
↑ Histone hyperacetylation.
↑ Insulin sensitivity.
↑ HDL-cholesterol.
↑ Neuroprotection.

The ketogenic diet has experimental evidence of cardio-protection by increasing tolerance to cardiac ischemia, reducing chronic low-intensity inflammation, decreasing oxidative stress, improving cardiac remodeling after ischemic injury and hypertension, and improving control of obesity, diabetes mellitus, and hypertension.[56-58]

The Mediterranean diet and the very low-calorie ketogenic diet have beneficial effects on gut microbiota that begin on the first day after starting the diet and peak after three months. Nevertheless, the ketogenic diet shows better results in body composition and gut microbiota profile.[59]

Exercise

Physical activity is a key part of treatment, either as primary or secondary prevention, and of rehabilitation programs in high cardiovascular risk and already diagnosed significant coronary atherosclerosis.[60,61] It can provide significant benefits in patients with myocardial ischemia with < 50% coronary stenosis with the following changes:[62,63]

↓ Weight.
↓ Fat tissue.
↓ Triglycerides.
↓ LDL-cholesterol.
↓ HbA1c.
↓ Major adverse events.
↓ All-cause mortality.
↑ HDL-cholesterol.
↑ Workload.
↑ Angina-score improvement.
↑ Depression-score improvement.

↑ Mean physical health score.
↑ Retinal microvascular health in children and adults.
↑ Microvascular function in the elderly's soleus.

Mental disorders

Anxiety and depression cause acute and chronic clinical and experimental coronary microvascular dysfunction, reduced coronary flow reserve, and impaired coronary endothelial function, especially but not exclusively in women.[64-66] Mental stress vasoconstriction results from the degradation of nitric oxide after endothelial nitric oxide synthase is downregulated and inactivated by stress hormones (glucocorticoids and pro-inflammatory cytokines and endothelin-1, amines, adhesion molecules, oxidized LDL particles, and so on), especially during maladaptive hypothalamic-pituitary-adrenal and sympathetic-adrenomedullary signaling pathway;[67,68] dysfunction of endothelial progenitor cells play an important role.[69,70] Stress and depression can lead to and cause endothelial and microvascular dysfunction with has been shown to increase cardiovascular morbidity and mortality. These mental disorders are associated with vicious cycles of vascular dysfunction, smoking, alcoholism, excessive carbohydrate intake, obesity, heart rate variability and arrhythmia, sedentism, and specific vitamin lack.[71-73] There is evidence of benefit after several psychological and psychiatric pharmacological and non-pharmacological interventions.[74-76]

Addictions

The known risk factors included in the metabolic syndrome (diabetes/pre-diabetes, hypertension, obesity, and dyslipidemia), together or separated, cause coronary microvascular disease. Other relevant lifestyle aspects include cigarette smoking, alcoholism, and opioid abuse.

Acute cigarette smoking causes a significant reduction of the coronary flow reserve measured by intracoronary Doppler, positron emission tomography, or transthoracic Doppler-echo of the left anterior descendant coronary artery through direct endothelial damage due to inflammation and oxidative stress.

Alcohol causes microvascular dysfunction through endothelial disorganization, degeneration, edema, perivascular fibrosis, sclerosis, inflammation, and increased capillary density; otherwise, opioids produce direct endothelial damage by nitric oxide counteraction and capillary density reduction. Cessation of these addictions may act on improvements.[77]

PHARMACOLOGIC TREATMENT

If MINOCA[78,79] or INOCA,[80,81] is not confirmed and an ischemic etiology is suspected, the patient can be stabilized with lower medication for a brief time.

Antiplatelet medication

Aspirin (75-300 mg) is an irreversible cyclooxygenase (COX-1) inhibitor in prostaglandin synthesis. COX-1 mediates the production of thromboxane A2 (TxA2) which induces platelet aggregation and vasoconstriction. The low-dose aspirin inhibits the production of TxA2.

↑ Vasodilation.
↓ Platelet aggregation.

Clopidogrel 75 mg, ticagrelor 90 mg, prasugrel 10 mg, orally and cangrelor 50 mg, intravenous are thienopyridines that inhibit adenosine diphosphate-induce, cause irreversible blockade of the P2Y12 receptor.

↓ Platelet aggregation.

Cilostazol 100 mg, inhibits collagen, 5'-adenosine diphosphate, epinephrine, and arachidonic acid, generates vasodilation in smooth muscle cells, and increases nitric oxide availability.

↑ Vasodilation.
↑ Antiplatelet properties.
↑ Anti-proliferative effects.
↓ Smooth muscle cell hyperproliferation.
↓ Intimal hyperplasia.

Dipyridamole 100 mg inhibits cyclic nucleotide phosphodiesterase, responsible for the degradation of adenosine monophosphate (AMP) to 5-AMP, which increases intra-platelet cyclic AMP reducing platelet aggregation, and blocks the uptake of adenosine by the platelets, increasing cyclic AMP.

↓ Platelet aggregation.
↓ Adenosine uptake.

Glycoprotein IIb/IIIa drugs block membrane glycoprotein IIb/IIIa platelet receptors, inhibiting fibrinogen binding. Indications: acute coronary syndromes (ACS), before and after PCI with or without stenting and stable angina.[82] The role of antiplatelet agents in the MINOCA setting is not well established.[83]

Anticoagulants

Anticoagulation is the first-line treatment for ACS, facilitating PCI and reducing cardiovascular disease complications, morbidity, and mortality. Thrombus is present in most ACS, including erosion, plaque fracture, and SCD. Unfractionated heparin (UFH), enoxaparin, fondaparinux, bivalirudin, and direct inhibitors of factor Xa are commonly used as adjuvants in pharmacologic or mechanical thrombolysis with antiplatelet agents.

↓ Mortality.
↓ Thrombosis cascade.
↓ Reduce the ischemic burden.
↓ Medication-related bleeding.
↓ Platelet activation.

There is no straightforward evidence of benefit for short or long-term use in the context of MINOCA or INOCA.[84,85]

Beta-blockers

There are major differences among beta-blockers. Lipophilic such as metoprolol, propranolol, and timolol have first-pass effects (metabolized in the gut wall and liver). Hydrophilic such as atenolol and esmolol which is absorbed in the gastrointestinal tract and excreted as active metabolites by the kidney. On the other hand, β_1 selectivity. They had antihypertensive and anti-ischemic actions, decreasing myocardial oxygen consumption, reducing heart rate and cardiac contractility, renin release, and angiotensin II production reduction, and improves left ventricular function. Beta-blocker is indicated in ACS, chronic stable ischemic heart disease, heart failure, arrhythmias, sudden cardiac death prevention, cardiomyopathies, valvular disease, myocardial bridging, hypertension, aortic dissection, vasovagal syncope, as well as secondary prevention, MINOCA, and INOCA.[86]

↓ Blood pressure.
↓ Cardiac output.
↓ Release of renin and production of angiotensin II.
↓ Presynaptic stimuli alfa adrenoceptors.
↓ Central vasomotor activity.
↓ Myocardial oxygen demand.
↓ Myocardial oxidative stress.
↓ Heart rate.
↓ Cardiac apoptosis.
↓ Platelet aggregation.
↓ Vascular smooth muscle cell proliferation.
↓ Cardiac contractility.
↓ Life-threatening arrhythmias.
↓ Mortality, including sudden cardiac death.
↓ Ischemia.
↓ Catecholamine-induced hypokalemia.
↑ Prolongation of diastole.
↑ Baroreflex function.
↑ Myocardial perfusion.
↑ Left ventricular structure and function.
↑ Fatty acids released from adipose tissue.

Calcium channel blockers (CCBs)

This is a heterogeneous group of drugs classified as Phenilalchilaminic (verapamil), dihydropyridines (DHP) amlodipine-like, or benzothiazepine (diltiazem), acts chiefly by vasodilatation and peripheral vascular resistance reduction. Verapamil and diltiazem act on nodal tissue and could be used in supraventricular arrhythmias. As secondary prevention, CCBs are indicated in exertional angina, myocardial ischemia, supraventricular arrhythmias, hypertension, vasospastic angina, INOCA, and postinfarction.[81]

↓ Stroke risk.
↓ Blood pressure.
↓ Voltage-dependent L-type calcium channel.
↑ Smooth muscle dilation.
↓ Inotropism.
↓ Chronotropism.
↓ Coronary spasm.

Angiotensin-converting enzyme inhibitors (ACEi)

These drugs produce vasodilatory effects leading to the increased local formation of bradykinin, the release of nitric oxide, and vasodilator prostaglandins, not observed with Angiotensin Receptor Blockers (ARB). ACEi are indicated in coronary artery disease, heart failure, ACS, and chronic kidney disease, associated or not with diabetes, MINOCA, and INOCA. Significantly reduces major cardiac events follow-up.[78-81]

↓ Adverse cardiac event.
↓ Blood pressure.
↑ Sympathetic-inhibitory effects.

Statins

Also known as 3-hydroxy-3methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors have several pleiotropic effects like anti-inflammatory, antihypertrophic, antifibrotic, and antioxidant properties, improve endothelial dysfunction, neurohormonal activation, and cardiac arrhythmias. Statins are indicated in primary and secondary atherosclerotic cardiovascular disease, coronary artery disease, ACS, vasospastic angina, MINOCA, and INOCA.[78-81]

Nicorandil

It is a vasodilator drug that increases the intracellular concentration of cyclic guanosine monophosphate (GMP). Beneficial effects are driven by the improvement of heart failure and ventricular arrhythmias. Nicorandil is indicated in the treatment of unstable or stable angina, INOCA, and PCI no-reflow phenomenon. It is available in tablets of 10 or 20 mg twice daily but also intravenously or intracoronary.[87]

Ranolazine

Inhibits the late phase of inward sodium channels, reducing intracellular sodium and calcium via the Na-Ca channel, and inhibits fatty acid oxidation, which enhances glucose oxidation, reduces lactic acid production, and improves heart function, does not affect heart rate or blood pressure. Ranolazine is indicated in the treatment of chronic stable angina and could be used in incomplete revascularization after PCI or CABG, INOCA, and as an adjunctive anti-arrhythmic agent in new or chronic atrial fibrillation. It is available in tablets of 500 mg twice a day.[88]

↓ Fatty acid oxidation.
↓ Lactic acid production.
↑ Glucose oxidation.
↑ Ventricular action potential duration.

Ivabradine

Lower heart rate by inhibiting if channels located in the sinoatrial node, without affecting other channels, consequently, does not affect myocardial contractility or vascular tone and reduces myocardial oxygen demand. Ivabradine is indicated in the treatment of heart failure, chronic stable angina, and INOCA. Is available in tablets of 5 and 7.5 mg twice a day.[89]

↓ Chronotropism.
↓ Myocardial oxygen demand.
↑ Diastolic time.
↑ Coronary circulation filling time.

Trimetazidine

It inhibits mitochondrial 3-ketoacyl coenzyme A thiolase, decreasing long-chain fatty acid β-oxidation, and improving mitochondrial metabolism with glucose oxidation stimulation. Its ant-ischemic action modulates cardiac metabolism without hemodynamic functions (coronary flow, contractility, blood pressure, or heart rate), has an anti-inflammatory profile, improves endothelial dysfunction, and limits membrane damage induced by reactive oxygen species. Trimetazidine is indicated for stable

angina, coronary interventions, pre or post-CABG, left ventricular dysfunction, diabetes mellitus, and INOCA. It is available in tablets of 35 or 80 mg twice or once a day.[90]

↓ Fatty acid oxidation.
↓ Glucose oxidation.
= Contractility.
= Blood pressure.
= Heart rate.

Long-acting nitrates

Activated by mitochondrial or cytosolic aldehyde dehydrogenase (ALDH2) into nitric oxide (NO), an endothelium-derived relaxing factor (EDRF), activates guanylate cyclase, increased cyclic guanosine monophosphate (cGMP) and causes vasorelaxation, and prevention of platelet aggregation and adhesion. Dilate venous capacitance vessels and coronary arteries, inducing venous pooling and preload reduction leading to a reduction of left ventricular end-diastolic filling pressure and wall stress, also decreasing right atrial pressure with a redistribution of blood from the central circulation into larger capacitance veins. Nitrate therapy is indicated in acute or chronic heart failure, stable coronary artery disease, acute coronary syndromes, arterial hypertension, and INOCA.[91]

↓ Preload.
↓ Left ventricular stress.
↑ Venous and coronary capacitance.
↑ Ventricular function.

Phosphodiesterase (PDE 5) inhibitors

These drugs are selective inhibitors of phosphodiesterase type 5 which increased cGMP and produces smooth muscle relaxation, and vasodilation, improving blood flow, providing benefits for both vascular and myocardial remodeling, attenuating hypertrophy, fibrosis, and impaired cardiac relaxation. The concomitant use of nitrates and other PDE inhibitors is contraindicated. PDE 5 inhibitor is indicated in erectile dysfunction, pulmonary hypertension, and INOCA.[92]

↑ Inotropic.
↑ Cardiac action potential.
↓ Blood pressure.
↓ Pulmonary arterial pressure.

Recommendation

1. Non-pharmacologic treatment must be the cornerstone in patients with MINOCA/INOCA.
2. Patients should stay under a multidisciplinary therapeutic approach including a cardiologist, nutritionist, psychiatrist, and psychologist.
3. The cardiologist must interact with nutritional advice for goals.
4. Improve lifestyle factors (diet, exercise, weight management, smoking cessation, and coping with stress.
5. Get in goals with hypertension, dyslipidemia, and diabetes.
6. In CAS, calcium channel blockers, long-acting nitrates, cilostazol, dipyridamole, PDE 5 inhibitors, nicorandil, and statins are indicated.
7. In MVD, ACE inhibitors, CCBs, nicorandil, long-acting nitrates, statins, beta-blockers, ivabradine, ranolazine, and trimetazidine, are indicated.
8. In MINOCA patients, statins, ACEi, and beta-blockers are indicated.
9. In INOCA patients, CCBs, long-acting nitrates, beta-blockers, nicorandil, statins, ACEi, PDE 5 inhibitors, trimetazidine, ranolazine, and ivabradine are indicated.

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