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Myocardial infarction with nonobstructive coronary arteries: from pathophysiology to therapeutic strategies

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Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous group of clinical entities characterized by clinical evidence of acute myocardial infarction (AMI) with normal or near-normal coronary arteries on coronary angiography (stenosis < 50%) and without an over the alternative diagnosis for the acute presentation. Its prevalence ranges from 6% to 11% among all patients with AMI, with a predominance of young, nonwhite females with fewer traditional risks than those with an obstructive coronary artery disease (MI-CAD). MINOCA can be due to either epicardial causes such as rupture or fissuring of unstable nonobstructive atherosclerotic plaque, coronary artery spasm, spontaneous coronary dissection and cardioembolism in-situ or microvascular causes. Besides, also type-2 AMI due to supply-demand mismatch and Takotsubo syndrome must be considered as a possible MINOCA cause. Because of the complex etiology and a limited amount of evidence, there is still some confusion around the management and treatment of these patients. Therefore, the key focus of this condition is to identify the underlying individual mechanisms to achieve patient-specific treatments. Clinical history, electrocardiogram, echocardiography, and coronary angiography represent the first-level diagnostic investigations, but coronary imaging with intravascular ultrasound and optical coherent tomography, coronary physiology testing, and cardiac magnetic resonance imaging offer additional information to understand the underlying cause of MINOCA. Although the prognosis is slightly better compared with MI-CAD patients, MINOCA is not always benign and depends on the etiopathology. This review analyzes all possible pathophysiological mechanisms that could lead to MINOCA and provides the most specific and appropriate therapeutic approach in each scenario.

Background

The most common pathophysiologic mechanism of acute myocardial infarction (AMI) is represented by atherosclerotic plaque rupture with subsequent intracoronary thrombus formation.[1]

However, following the increased use of coronary angiography in patients with AMI in the last two decades and the broadening of AMI diagnosis even in patients with only mild troponin increase as a marker of myocardial necrosis, myocardial infarction with nonobstructive coronary arteries (MINOCA) appears to be increasingly recognized in daily clinical practice.[2]

The first case of MINOCA dates back >75 years, when an autopsy revealed myocardial necrosis without significant coronary atherosclerosis. DeWood *et al.* reported, in their angiographic studies, an approximately 5% prevalence of nonobstructive coronary artery disease among patients with AMI.[3,4] A meta-analysis, which included 28 studies from 1995 to 2013, reported an overall prevalence of 6–8% with variations depending on the proportion of patients who underwent coronary angiography and on the assay used for high-sensitivity cardiac troponin measurement.[5–7] In a recent multicenter study of young patients (aged 18–55 years), MINOCA showed a prevalence of 11%.[8] Compared with AMI and obstructive coronary artery disease (CAD), MINOCA presents some peculiar epidemiological features. Subjects are younger, show a predominance of women and nonwhite patients and present fewer traditional risk factors and previous or

Fig. 1
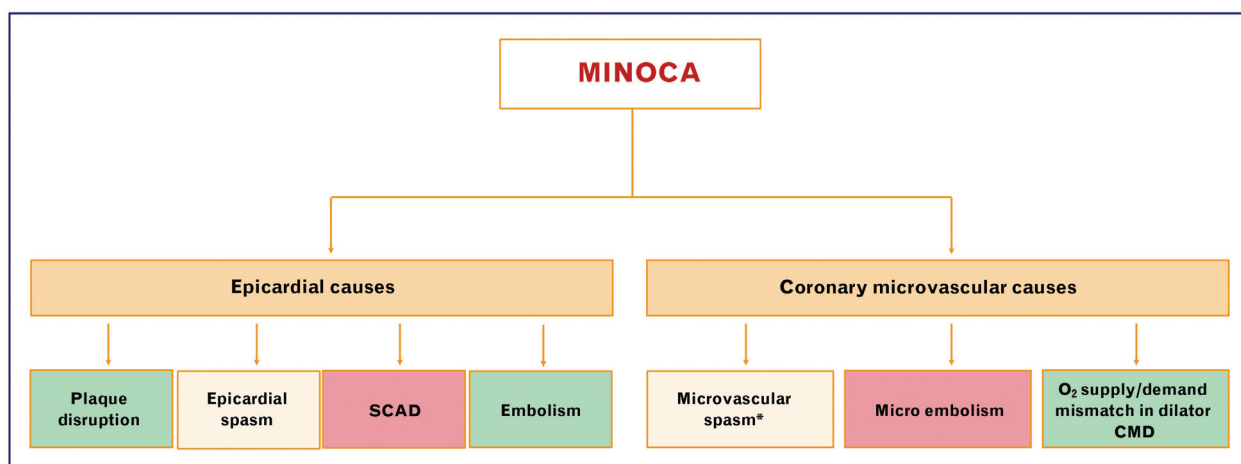
Coronary mechanisms for MINOCA. AMI, acute myocardial infarction; SCAD, spontaneous coronary artery dissection; CMD, coronary microcirculation dysfunction. *In some patients microvascular spasm might result in a takotsubo syndrome.

concurrent cardiovascular diseases, except for hypertension, which seems to be equally shared by MINOCA and MIOCA patients.[2,9] Despite initial considerations, more extensive long-term studies have demonstrated that MINOCA prognosis is not benign, with an increased long-term risk of all-cause mortality and major adverse cardiovascular events (MACE) similar to the data observed in MI-CAD patients.[10,11]

However, MINOCA has heterogeneous causes which may result in different and variable prognostic implications (Fig. 1). Accordingly, to apply the most appropriate form of treatment, it is important to clarify the specific underlying pathophysiological mechanism of the syndrome in individual patients.[12] In this review, we discuss the different pathophysiological pathways that lead to MINOCA and evaluate the best therapeutic approach in each scenario.

Definition and diagnosis of myocardial infarction with nonobstructive coronary arteries

In 2016, the European Society of Cardiology proposed the following criteria for the diagnosis of MINOCA: AMI criteria, as defined by the 'Third Universal Definition of Myocardial Infarction'; the presence of nonobstructive coronary arteries disease, that is, no stenosis ≥50% in any epicardial vessel; and no other clinically obvious specific cause that might provide an alternative diagnosis for the acute presentation.[13]

Importantly, although elevated troponin levels indicate myocyte damage, the process is not disease specific and can result from either ischemic or nonischemic conditions. Therefore, with the 'Fourth Universal Definition of Myocardial Infarction' the concept of myocardial injury

was redefined and the diagnosis of MINOCA was also revised.[1] Specifically, in case of suspected AMI and absence of obstructive CAD, alternative causes of elevated troponin levels, such as sepsis, pulmonary embolism, and myocarditis, should be excluded. Among the above, the most challenging confounder is represented by acute myocarditis presenting with chest pain, which is often associated with ST-segment deviation, perfectly mimicking an AMI. Therefore, the diagnosis of MINOCA should be considered as a working diagnosis until other possible causes are ruled out.[12]

MINOCA can present both as a type-1 or type-2 AMI. Clinical history, electrocardiogram, cardiac biomarkers, echocardiography, and coronary angiography represent the first-level diagnostic tools to confirm or exclude the diagnosis.[14] Additional coronary imaging or physiologic studies may be necessary when angiography is nondiagnostic. Invasive coronary imaging with optical coherence tomography (OCT) and intravascular ultrasound (IVUS) allows a detailed examination of the vascular layers and plaque structure. Instead, the assessment of coronary physiology with pharmacologic provocation testing may identify abnormalities in epicardial and/or microvascular vasomotor function that can be responsible for myocardial ischemia when no other apparent cause of AMI is identified. Of note, a relevant role in the diagnostic workup of patients with an acute clinical presentation with suspected MINOCA is played by cardiac magnetic resonance (CMR).[12]

CMR is particularly helpful in cases of uncertain diagnosis, thanks to its ability to differentiate ischemic versus nonischemic myocardial damage.[15–17] Late gadolinium enhancement (LGE) with sub-endocardial or transmural distribution and regional coronary injury indicates an

ischemic cause, whereas nonischemic LGE patterns (sub-epicardial or intra-myocardial) suggest a cardiomyopathy or myocarditis.[18,19] Finally, the absence of relevant LGE with myocardial edema associated with specific wall motion abnormalities (e.g. apical ballooning) is indicative of Takotsubo syndrome (TSS) (see thereafter).[20]

Mechanisms and specific therapy of myocardial infarction with nonobstructive coronary arteries

Plaque disruption

Disruption of noncritical atherosclerotic plaques, including plaque erosion, ulceration, and rupture, is an important cause of MINOCA and may accounts for 5–20% of cases (Fig. 1).[21,22]

Myonecrosis in these patients can be mediated by transient thrombosis, thromboembolism, superimposed vasospasm, or a combination of these processes. Spontaneous thrombolysis or autolysis of a coronary thrombosis has been proposed to explain the absence of suboccluisive or occlusive thrombi at coronary angiography in MINOCA, especially when coronary angiography is performed late and antithrombotic as well as antiplatelet agents have been promptly administered.[23]

Among MINOCA patients with subcritical plaque disruption, CMR imaging may show large areas of myocardial edema with or without small areas of necrosis, suggesting that flow has been only transiently impaired in a large vessel. Alternatively, CMR may reveal a smaller, well defined LGE area, related to a smaller vessel, suggesting embolization of ather-othrombotic debris from the rupture site as the most likely mechanism of myonecrosis.[21]

The angiographic features that may indicate plaque rupture include mild vessel narrowing (<50%), asymmetrical lesions, narrow neck, irregular edges, haze or radiolucent flap.[13,24,25]

Despite the abovementioned angiographic findings, coronary angiography has important limitations.

Plaque lesion, therefore, can only be definitively diagnosed with intracoronary imaging, that is, high resolution OCT and IVUS.[25] Importantly, this multidimensional invasive coronary evaluation may also allow thrombi that can be missed to be visualized during a coronary angiography. Furthermore, techniques to assess the functional significance of epicardial coronary stenosis, such as fractional flow reserve (FFR), are increasingly used to exclude the ischemic potential of angiographically subcritical stenosis.[12,27]

Importantly, however, it has been suggested that atherosclerotic plaques may undergo complications and elicit acute coronary syndromes (ACSs) when they exhibit some peculiar histopathologic characteristics (i.e. thin fibrous cap, predominant lipid content, etc.) that do not necessarily match with angiographically significant stenosis. Several previous studies showed that AMI more frequently occurs following coronary thrombotic occlusion at the level of subcritical coronary plaques. Interestingly, in a study, angiographically mild lesions at baseline were found to be responsible for almost 12% of MACE at 3 years of follow-up.[28] Most recently, among 145 women with MINOCA, OCT identified some epicardial plaque abnormalities possibly responsible for the ACS in 46.2% of cases.[29] Precious information regarding the functional ischemic status of patients with non-ST-segment elevation myocardial infarction (NSTEMI) and nonobstructive CAD derives from the FAMOUS Trial.[30] In fact, among the subjects with coronary stenosis <50%, 6.8% exhibited a functional significant (FFR ≤ 0.80) lesion and were all managed with optimal medical treatment.

The documentation or suspicion of acute coronary plaque complications as a cause of MINOCA portends relevant therapeutic implications. These patients should indeed be treated in the same way as patients with type-1 AMI. Thus, dual antiplatelet therapy (DAPT) should be recommended for 1 year, followed by single lifetime antiplatelet treatment. In fact, an observational retrospective cohort study of MINOCA patients enrolled in the SWEDEHEART registry found no prognostic benefit of DAPT administration.[31–33] However, this disappointing result was obtained in the whole MINOCA cohort, while DAPT can be expected to improve prognosis only in patients with a thromboembolic cause of MINOCA.

Thus, in a pilot study, Prati *et al.* compared the efficacy of DAPT versus angioplasty and stenting in 31 patients with OCT-detected culprit plaque erosion, showing a low rate of adverse events and revascularization in patients treated with DAPT alone.[34] The EROSION study confirmed this finding, as DAPT with aspirin and ticagrelor was associated with a significant reduction in thrombus volume and a low rate of adverse events at 30 days. Furthermore, at 1-year follow-up, 92.5% of patients with AMI caused by plaque erosion managed with DAPT without stenting remained free of MACE. However, these studies included both obstructive and nonobstructive lesions without indication of the exact number of nonsignificant lesions (stenosis < 50%) and had surrogate primary endpoints. Thus, their data should be confirmed in dedicated randomized clinical trials (RCTs) of MINOCA patients powered for clinical outcomes.[26,27] A recent meta-analysis aggregated data from two studies to assess the impact of DAPT on outcomes of MINOCA patients over a median follow-up of 24 months.[35–37] According to their results, DAPT was associated with a significant reduction of all-cause death in patients with MINOCA [hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.55–0.98]. However, this meta-analysis evaluated only two studies with a very different weight (98.6% vs. 1.4%). Furthermore, in one study only CMR was performed to discriminate between ischemic or alternative patterns of myocardial damage, as in TSS or myocarditis.

In summary, currently there is no evidence of benefit of routine administration of DAPT in the whole population of MINOCA patients. Future studies, however, should establish the effects of DAPT in patients with MINOCA specifically caused by transient thrombosis on disrupted, nonsignificant coronary plaques.

Of note, in a post-hoc analysis of the CURRENT-OASIS 7 randomized trial, high dose of clopidogrel also did not appear to offer any additional benefit than a standard dose of clopidogrel in patients with MINOCA as opposed to in patients with obstructive myocardial infarction.[38]

Together with DAPT, beta blockers might be suggested to be of benefit in patients with MINOCA caused by thromboembolic mechanisms, as in the whole population of AMI.

It is widely recognized that AMI patients exhibit an increased sympathetic activation which might play a significant role in the occurrence of cardiovascular events,[39] and beta blockers may improve clinical outcomes by contrasting the negative effects of the sympathetic nervous system on the infarcted and ischemic myocardium, mainly by reducing myocardial oxygen requests and increasing myocardial resistance to ischemic injury.

Current recommendations for using beta blockers in the whole population of AMI patients are not univocal. American guidelines, indeed, recommend routine treatment with beta blockers, whereas European guidelines restrict the recommendation to patients with heart failure or left ventricular systolic dysfunction.[40,41] As far as MINOCA is concerned, it should be highlighted that no RCT has yet evaluated the effect of beta blocker treatment in this specific setting.[41,42] Lindahl *et al.* showed that beta blocker treatment in MINOCA patients was associated with a 14% reduction in MACE, even if no statistical significance was reached.[37] Furthermore, a multicenter national registry demonstrated that during a median follow-up of 8.5 years, the use of beta blockers was associated with a low frequency of MACE in MINOCA patients.[43]

Another class of drugs routinely administrated following AMI is represented by renin–angiotensin–aldosterone system (RAAS) inhibitors. These drugs, in particular angiotensin-converting enzyme inhibitors, were shown to improve survival in several RCTs of AMI patients.[44,45] Accordingly, ESC guidelines recommend the use of RAAS inhibitors for effective protection of patients with and without ST-segment elevation MI, specifically among those with impaired LV function or some associated conditions, such as hypertension or diabetes.[31,40] In the setting of MINOCA, the beneficial effect of RAAS inhibitors has been suggested by many observational studies even though some limitations should be considered, such as the variable definition of MINOCA and the inclusion of patients with nonischemic causes of troponin elevation.[36,37] Thus, their use should probably be restricted to MINOCA patients with well defined indications to RASS, such as those described above.

Finally, statin therapy should be prescribed to patients with MINOCA caused by thromboembolic complications.[22] The benefit of statins in the whole population of patients with AMI is, indeed, well defined. While RCTs in MINOCA patients are lacking and observational studies have shown discordant results, a recent meta-analysis showed a favorable impact on long-term outcomes[36,37,42,44,46,47] and in the SWEDEHEART registry, statins reduced most cardiovascular end points, including all-cause mortality.[37] In the setting of athero-thrombotic MINOCA, statins likely act by stabilizing unstable plaques, which are rich in lipid content. This effect is achieved by reducing lipid levels (which is the crucial goal of statins), but also through pleiotropic mechanisms of statins, including antiinflammation, antioxidant and antithrombotic effects.[48] The use of the anticholesterolemic drugs ezetimibe and PCSK-9 should also be considered in patients with MINOCA of athero-thrombotic origin in case of intolerance to statins or insufficient control of cholesterol levels.[29,41,49,50]

In summary, in patients with MINOCA caused by thromboembolic mechanisms at the level of disrupted plaques, treatment should follow the same indications as are valid for the whole population of AMI patients.[36,42,46,51]

Coronary embolism and hypercoagulative state

Coronary artery embolism (CAE) may result in myocardial necrosis, in absence of any angiographic evidence of coronary flow-limiting lesions, by occluding a distal coronary branch or small resistance arteries of coronary microcirculation. CAE can result in MINOCA when the stenosis is $< 50\%$ of the coronary lumen. The prevalence of CAE in autoptic studies ranges from 4% to 13% and a recent clinical retrospective study suggested that CAE accounts for approximately 3% of all ACS.[50,52,53] Single small emboli or multiple microemboli can derive from the lysis of angiographically visible or nonvisible partial non occlusive thrombi formed on disrupted nonsignificant epicardial plaques (see above), but direct coronary embolism may originate from a thrombus located in the left atrium, left ventricle, or pulmonary veins. Furthermore, infective or noninfective endocardial vegetations of the aortic or mitral valves, as well as intracardiac tumors, can also be responsible for CAE and MINOCA,[54–59] which, in rare cases, can also be caused by paradoxical embolism due to right–left intracardiac shunts, mainly related to the presence of patent foramen ovale (PFO).[60]

Finally, iatrogenic CAE may occur as a consequence of clot formation on catheters during prolonged invasive coronary or intracardiac procedures, in particular when a correct anticoagulation is not maintained and/or catheters are not well flushed. Of note, nonthrombotic material

– such as calcifications, fatty emboli and gas – may also result in CAE during invasive procedures.[61–64]

The pathophysiologic mechanisms of CAE can be classified into three categories: direct, paradoxical, and iatrogenic, with some overlap among these forms.

Importantly, hypercoagulable states, deriving from either hereditary or acquired disorders, have also been associated with a higher risk of CAE, as a result of coronary or extra-coronary thrombi embolization.[12,22] A systematic review examining the use of thrombophilia testing in MINOCA has reported a 14% prevalence of inherited disorders, with factor V Leiden and activated protein C resistance being the most observed conditions, followed by protein C or S deficiency.[37] Acquired thrombophilia disorders potentially associated with increased risk of CAE include thrombotic thrombocytopenic purpura (TTP), autoimmune disorder antiphospholipid syndrome, heparin-induced thrombocytopenia (HIT), and myeloproliferative neoplasms.

CAE involving a distal epicardial vessel is characterized, at coronary angiography, by a sudden cut-off sign.[14,50] Additional imaging with IVUS or OCT may further confirm the diagnosis, but they are rarely performed due to the risk of further distal embolization.

Transthoracic, transesophageal and bubble contrast echocardiography are useful methods to identify cardiac sources of embolism, particularly in the search for atrial septal defects.

The treatment of CAE should be individualized and depends on multiple factors, including patient characteristics, time of presentation and the presence or absence of other embolic sites. All subjects with MINOCA caused by CAE should receive anticoagulant therapy, probably with one of the oral anticoagulant drugs.[65] Anticoagulation should be continued for 3 months in the absence of procoagulant or persistent risk factors, whereas, if persistent CAE risk factors are present, long-term oral anticoagulation should be considered. In paradoxical CE, PFO closure can be performed percutaneously.

Anticoagulant therapy may finally be appropriate for preventing embolic events in left-side origin coronary embolism or for long-term treatment.[14]

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is becoming an increasingly recognized cause of ACS, with an estimated prevalence ranging from 1.7% to 4%.[66] SCAD can provoke the complete occlusion of the coronary artery, although when the stenosis is <50%, SCAD can be a cause of MINOCA. SCAD usually occurs in absence of significant coronary atherosclerosis and is more common in females, accounting for 25% of all ACS cases in women under the age of 50 years.[67–69] The typical feature of SCAD is represented by a false lumen within the coronary artery wall that can compress the true lumen, causing ischemia.[70]

Several conditions have been related to SCAD, including factors that make coronary wall structures more prone to dissection and stressors that may serve as triggers of the dissection. Some risk factors for SCAD recurrence have been identified, such as hypertension, fibromuscular dysplasia, anatomical variations of the coronary arteries, and migraine.[70–73] The peripartum period is a predisposing condition due to changes in the intima-media composition of vessels related to the rise in hormonal levels of progesterone. Furthermore, an association with vascular collagen disorders, chronic inflammatory diseases and periadventitial eosinophil infiltrate has been described.

A positive feature of SCAD is that it often heals spontaneously, which typically occurs at an early stage (within a few days). However, recurrence of myocardial ischemia from SCAD is associated with a higher risk of MACE.

Coronary angiography is the primary diagnostic tool for SCAD and, based on the angiographic pattern, SCADs can be divided into three types. The detection of a double image of the lumen defines type 1 lesions. Type 2 lesions are characterized by a long narrowing of the lumen, usually longer than 20 mm. Lastly, type 3 lesions are identified by an abrupt focal narrowing (lesion length <20 mm), which can mimic an atherosclerotic stenosis.[67,68,74] In a large SCAD registry, Saw et al. showed that the most commonly observed angiographic pattern was type 2 (67.0%), followed by type 1.[75]

CTCA may reveal abrupt narrowing of the lumen and the finding of intramural hematoma. Unfortunately, the sensitivity of CTCA is not optimal due to its poor spatial resolution.[76] In the presence of type 1 lesions, the angiographic features associated with clinical and demographic variables are sufficient to reach a diagnosis. However, both IVUS and OCT can be helpful, especially in type 2 and 3 dissections.

In terms of treatment, the first-line approach consists of a conservative medical therapy, while coronary revascularization can be indicated only in cases of occluding lesions, high-risk anatomical features (involvement of severe proximal sites in the left main coronary artery or proximal left anterior descending artery), low-grade thrombolysis in myocardial infarction (TIMI), ongoing myocardial ischemia with hemodynamic instability or disease refractory to medical treatment.[77] Stent implantation has indeed been associated with an increased risk of complications, due to the propagation of the vessel dissection. When PCI is indicated, a cut balloon dilation (with or without stent) may be a reasonable option.[78]

After clinical stabilization, long-term management of SCAD is aimed at reducing chest pain and preventing recurrences. Treatment includes antianginal therapy for ongoing chest pain, hypertension control and stress

management.[65] Beta blockers are generally recommended in both acute and long-term treatment strategies of SCAD, due to the reduction of arterial shear stress and the potential prognostic benefit.[79–82] The use of other drugs, such as RAAS inhibitors or statins is questionable in SCAD. RAAS have not been tested, while a retrospective study from the Mayo Clinic group suggested a slightly increased risk of relapse in patients treated with statins.[72] Similarly, the use of antiplatelet therapy remains controversial. A rationale for the use of single or dual antiplatelet therapy is the potential risk of thrombosis at the level of the compressed true coronary lumen even though some researchers argue that the intimal tear may act as a prothrombotic stimulus. However, antiplatelet agents present a theoretical increased risk of bleeding and propagation of the dissection.[2,67] Data from the 'DIssezioni Spontanee COronariche' (DISCO) registry suggest that in conservatively managed patients, DAPT may indeed be associated with an increased risk of MACE compared with single antiplatelet therapy, thus indicating that at least DAPT should be avoided in SCAD patients.[83]

According to expert consensus, in the context of ACS due to angiographically documented SCAD, anticoagulation therapy should be discontinued.[77,84] Finally, it has been reported that SCAD may be associated with some inflammatory conditions. Therefore, low-dose anti-inflammatory therapy such as colchicine may be effective in preventing recurrences, particularly in inflammation-related SCAD phenotypes.[85]

Coronary artery spasm

Coronary artery spasm (CAS) is a transient and intense constriction of epicardial coronary arteries related to a vasal smooth muscle hyperreactivity to endogenous or exogenous constrictor agents, like high exposure to air pollution.[86] In most patients, a coronary endothelial dysfunction, which favors the constrictor response, can be also demonstrated.

Variant angina is the most frequent clinical presentation of CAS. Unlike the classical exercise-induced angina pectoris, in variant angina chest pain occurs at rest, often during sleep or in the early morning, irrespective of myocardial oxygen demand, although exercise may also trigger CAS and angina in a sizeable proportion of patients. CAS in variant angina occurs in normal or near-normal epicardial vessels in about 50% of patients. Therefore, MINOCA may occur in these patients when an episode of prolonged CAS results in ischemic myocardial injury.[87] In fact, although variant angina is the most common clinical manifestation of CAS, in some patients a single intense and prolonged episode of CAS can also be responsible for a MINOCA.[88] It is worth mentioning that CAS can even be detected in patients with biopsy-proven parvovirus B19-induced myocarditis, perfectly mimicking a MINOCA. Possible mechanisms responsible for such vasospasm relate to an increase in oxidative stress, a reduction in the bioavailability of vasodilator nitric oxide and consequent endothelial dysfunction.[89]

Although the diagnosis of MINOCA related to CAS is rather easy to achieve in patients with a documented history of variant angina, the demonstration of CAS as a cause of MINOCA in patients without any previous or ongoing history of vasospastic angina requires provocative tests during coronary angiography, such as intracoronary administration of acetylcholine (Ach) or intravenous or intracoronary administration of ergonovine. In a recent prospective study, Ach provocation testing was associated with a low risk of complications, with no differences between INOCA and MINOCA patients.[90]

The prevalence of sporadic CAS as a cause of MINOCA, as assessed by provocative tests (mainly Ach test) varied across the studies, ranging, in a recent meta-analysis, between 3% and 95%. This wide difference depended on multiple factors, including the definition of CAS, the ethnic origin of patients and the stimuli used to reveal CAS. Moreover, the prevalence was 28% when CAS was defined as a reduction of $\geq$50% or 75% of the coronary lumen at angiography and 34% when the vasospasm rate was clinically defined as the development of chest pain, typical ischemic ST-segment changes or echocardiographic regional wall motion abnormalities.[5] In a recent study on MINOCA patients, Montone *et al.* reported that 30% of MINOCA patients had evidence of CAS in response to an Ach test.[91]

Management of CAS involves some lifestyle changes, aimed to eliminate conditions that may favor CAS induction, including, in particular, smoking cessation and consistent reduction of alcohol consumption, together with avoiding the use of some substances and drugs, such as cocaine, sympathomimetic agents, beta blockers, parasympathomimetic agents, ergot alkaloids and the chemotherapic 5-fluoro-uracil.[14,92] Although CAS may be quickly relieved by short-acting nitrates, calcium channel blockers (CCBs) constitute the standard long-term treatment.[93–96]

CCBs usually suppress angina symptoms and improve clinical outcomes in CAS patients. Accordingly, withdrawal of an effective CCB therapy can be deleterious in such patients. In a recent study on MINOCA patients, two-thirds of all deaths and ~60% of cardiac deaths occurred among patients who showed a positive provocative test for CAS who initially received CCBs, but reduced or discontinued treatment during follow-up.[91]

Long-acting nitrates can be added to CCBs to treat CAS, although their effects on CAS prevention are limited due to the development of tolerance. To overcome this problem, when associated with CCBs, nitrates should be given in an asymmetrical way during the day, in order

to cover the period with the highest occurrence of angina attacks and leave a nitrate-free period to restore vascular sensitivity to their dilator effect. A few studies have suggested that the addition of statins to vasodilator therapy may improve symptom control and outcome in CAS patients, thanks to their pleiotropic effects, mainly the improvement in endothelial function as a result of decreased oxidative stress and inflammation. In patients with CAS-induced MINOCA included in the Korea AMI Registry (KAMIR), statin therapy significantly reduced the risk of the composite primary end point, and similar findings were found in another observational study of MINOCA patients. Both studies, however, were nonrandomized.[37,97] Furthermore, previous studies failed to show favorable effects on clinical outcome of statins in patients with vasospastic angina. Thus, statins cannot be recommended at present in MINOCA caused by CAS, unless indicated for other reasons.

In MINOCA patients with evidence of coronary spasm, routine prescription of antiplatelet therapy is not recommended. Even if a link has been proposed between episodes of coronary vasospasm and platelet activation and aggregation in the coronary circulation, such therapy has not been demonstrated to improve clinical outcomes in CAS patients and might actually even aggravate symptoms and outcomes.[98,99]

Coronary microvascular spasm

Coronary microcirculation dysfunction (CMD) is defined as the presence of abnormalities in the function of coronary microcirculation due to smooth muscle cell and/or endothelial abnormalities of small resistance coronary arteries. CMD is often associated with diabetes, hypertension and heart failure with preserved ejection fraction and can frequently be responsible for a chronic form of exercise/LV hypertrophy-induced angina, defined as microvascular angina, resulting from an imbalance between the increase in oxygen demand during exercise and the blunted increase in coronary blood flow (CBF) caused by a reduced vasodilation of coronary microcirculation.[47,100–102] CMD, however, may also predispose to vasoconstriction or spasm of small resistance arteries (coronary microvascular spasm, or CMVS), which can result in ACS and MINOCA. CMVS can occur as the effect of some acute vasoconstrictive triggers, such as a heightened adrenergic activation, acting on basically dysfunctional resistance arteries.

In recent years, it has become clear that abnormalities of coronary microcirculation can result in myocardial ischemia. Multiple invasive and noninvasive investigations have been proposed to evaluate CMD.[103] The role of CMVS in causing MINOCA can be assessed, again, by provocative tests of spasm performed during invasive coronary angiography. In patients with a tendency for CMVS, the administration of constrictive agents (i.e. Ach or ergonovine) results in typical chest pain and ischemic

ECG changes, but without any evidence of epicardial spasm.[104] More directly, the recording of CBF velocity by intracoronary Doppler might document a reduction in CBF during Ach/ergonovine administration. The tendency for CMVS in MINOCA patients has hitherto been assessed in only two studies with some relevant difference. Montone *et al.*, in the previously cited study, among 80 patients with suspected MINOCA, showed a rate of CMVS of 16%, whereas Pirozzolo *et al.*, in 96 similar patients, found Ach test positivity for CMVS of 31%.[105]

In MINOCA patients in whom invasive assessment for the induction of CMVS was not performed, the presence of CMD, suggesting its role in the MINOCA presentation, can be assessed by investigating the dilator microvascular function using noninvasive methods, mainly PET and CMR, but also transthoracic echo-color-Doppler of the left anterior descending coronary artery. A coronary flow reserve (CFR) <2.0, as calculated by the ratio between CBF at peak of adenosine administration and baseline CBF by PET or CMR, or even as the ratio between peak adenosine to baseline CBF velocity with echo-Doppler-based measurements, definitely identifies CMD, with CFR values between 2.0 and <2.5 also suggesting CMD.[106] Of note, a noninvasive ergonovine test resulting in reduced CBF velocity may also suggest increased coronary microvascular constriction in MINOCA patients, although a contribution of epicardial constriction cannot be excluded. Microvascular function can be specifically estimated with the thermodilution-based index of microvascular resistance (IMR).[91]

The optimal treatment for patients with CMVS is still undefined. Similarly to CAS, CCBs should be considered the first-choice class of drugs, but whether their efficacy is similar to that demonstrated for CAS remains to be determined, although some preliminary data in patients with microvascular unstable angina suggested encouraging results. Nitrates can also be administered in MINOCA caused by CMVS, but their effect on coronary microcirculation is questionable and might also be detrimental.[107]

Finally, whether some types of drugs that showed good results on chronic exercise-induced microvascular angina, including RASS inhibitors and statins, may be of some benefit in CMVS-induced MINOCA remains unexplored.[108] The beneficial effects of RASS inhibitors and statins for secondary prevention in MINOCA patients have been reported, although, no distinction on the underlying pathophysiological mechanism was made.[56,109]

Takotsubo syndrome

It is still controversial whether TTS should be classified as a particular form of MINOCA or a separate entity, due to its specific clinical characteristics and the still undetermined pathophysiologic mechanisms.

TTS, also defined as stress-induced cardiomyopathy, is a condition mimicking an ACS/AMI, typically triggered by emotional or physical stress.[110] Together with this anamnestic finding, TTS patients present a typical global medio-distal akinesia, with preserved contractility of the basal segments of left ventricle.[111]

The prevalence of TTS is estimated to be approximately 2–3% among patients presenting with suspected ACS.[112] The precise pathophysiological mechanisms of TTS are incompletely understood, but there is considerable evidence that sympathetic stimulation plays a central role in its pathogenesis. In most cases, TTS has been associated with conditions characterized by an excess of catecholamines such as emotional, physical, or surgical stress or pheochromocytoma. However, the mechanism by which catecholamines precipitate the myocardial stunning in the variety of regional ballooning patterns that characterize the syndrome is unknown.[113] The main mechanisms proposed are plaque rupture followed by rapid lysis, sympathetically mediated epicardial spasm, diffuse CMVS and direct cardiotoxicity of catecholamines.[108–114]

Some triggering factors have been identified; the preponderance of postmenopausal females among TTS patients suggests that a hormonal state characterized by low estrogen levels may predispose to TTS in women. Neurologic or psychiatric conditions may also serve as predisposing factors for the development of TTS.[115]

Although apical ballooning constitutes the most common and known type of LV impairment in TTS,[116] several variants of regional LV contractile impairment, such as midventricular, basal and focal, have been increasingly recognized.[117]

In the typical time course of TTS, ST-segment elevation is observed at onset, followed by deep and widespread T-wave inversion with significant QT prolongation.[118] Biomarkers of myocardial injury are elevated in most patients with TTS. However, their levels are disproportionately low when compared with the extent of wall motion abnormality.[115] Patients with a suspected TTS should immediately undergo coronary angiography to confirm the diagnosis by showing no significant CAD and confirming the typical impairment of left ventricle function. Echocardiography is useful to detect typical TTS findings and is the elective cardiological test to assess the evolution of LV function over time. CMR, however, may be superior to echocardiography to evaluate regional wall motion abnormalities, and CMR findings in TTS patients include myocardial edema, showing high signal intensity in T2-weighted images in the same region of the wall motion abnormality. Classically, the absence of LGE is an important criterion of TTS.[119]

There are no RCTs on the specific treatment of TTS. Beta blockers are intuitively the most logical pharmacotherapy for prevention of TTS recurrence. However, recently it has been demonstrated that the use of beta blockers in patients with TTS after discharge did not have a beneficial effect on short-term prognosis or on preventing recurrence.[115,120] RAAS inhibitors are the only drugs associated with reduced recurrence rate of TTS or improved survival at 1-year follow-up.[114,120] Their beneficial effects are probably the result of sympathetic activity reduction through the renin–angiotensin system, the anti-inflammatory effect on the myocardium or their positive effect on endothelial and coronary microvascular function.

## Oxygen supply/demand imbalance myocardial infarction

In some patients, ischemic myocardial necrosis in patients without obstructive CAD may occur as a result of an imbalance between myocardial oxygen supply and demand, in absence of any evidence of specific mechanisms causing a dramatic reduction in CBF. This type of AMI (classified as type 2 AMI) usually results from systemic conditions which determine an increase in myocardial oxygen demand and/or impaired oxygen delivery (e.g. sepsis, tachyarrhythmias, anemia, hypotension, hypoxia), usually in the presence of CMD or epicardial vasoconstriction. This population is typically older, with a predominance of women, and exhibits more comorbidities compared with patients with AMI caused by athero-thrombotic disease.[121,122,123] The management of type 2 MINOCA should be based on treating the basal conditions and removing the triggering cause(s), while long-term therapy should be decided after an adequate assessment of cardiac conditions after the acute phase.

Knowledge gaps

Despite significant improvements in the management of AMI patients, several knowledge gaps still exist in the hazy world of MINOCA. Indeed, in this heterogenous population it is essential to search for the specific pathophysiological mechanism(s) responsible for the acute clinical presentation, which may allow the selection of the most appropriate treatment.[124–126] Thus, we propose that the generic term of MINOCA should be abandoned and studies including patients with any type of MINOCA should be avoided. We propose, instead, that the term MINOCA should be followed by the mechanisms responsible for the acute event (e.g. MINOCA due to plaque disruption, MINOCA due to CAE, MINOCA due to CAS, MINOCA due to CMVS, etc.). The term MINOCA of undefined cause could be used to indicate MINOCA in which a definite identification of the cause was not achieved. Figure 2 shows the different diagnostic workup and the most appropriate management for each MINOCA mechanism.

Another unresolved issue is the identification of high-risk phenotypes and, possibly, prognostic predictors that may help to improve in-hospital management as well as

Fig. 2
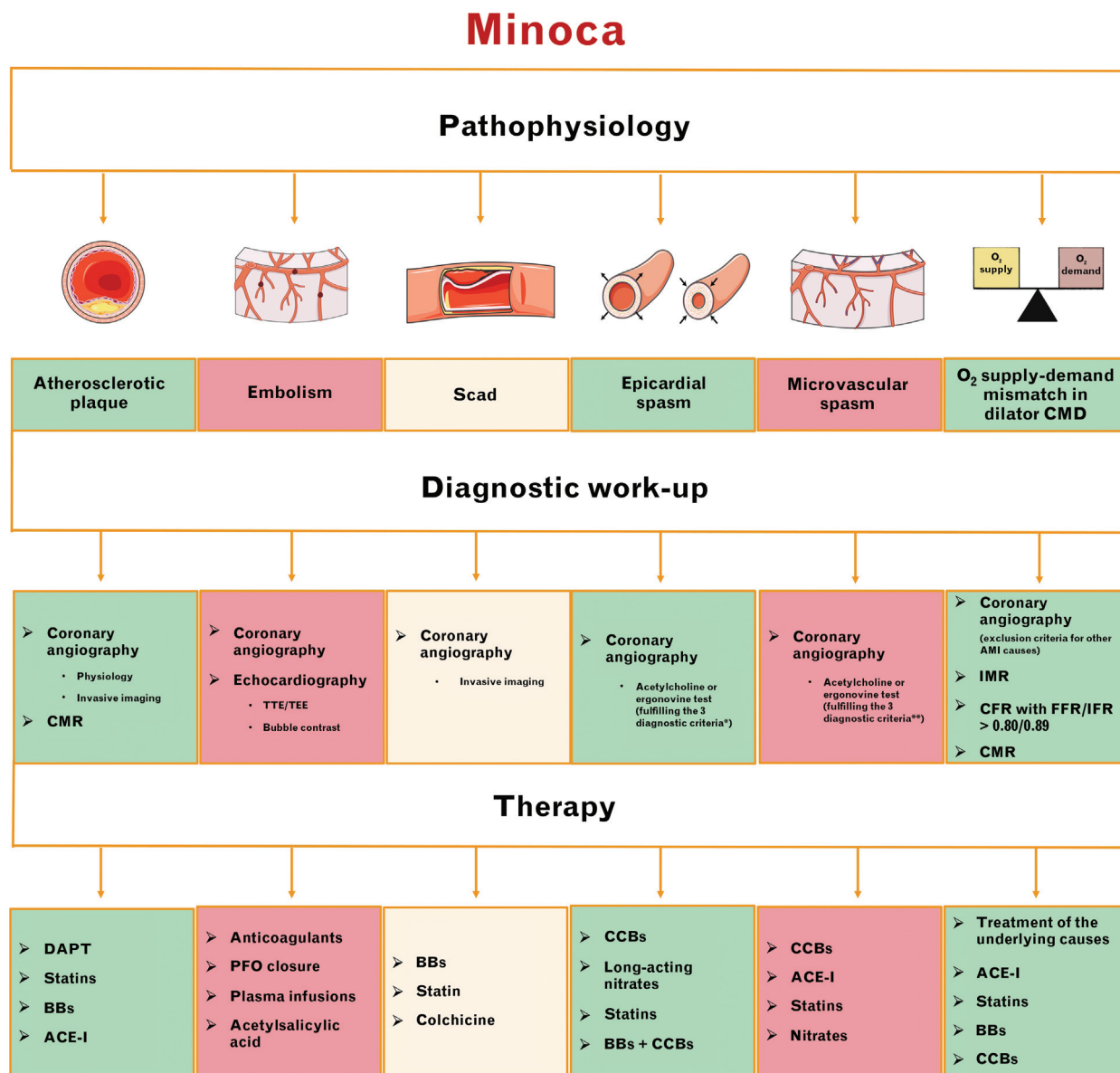
Minoca

Diagnostic workup and management for MINOCA based on underlying mechanism. ACEi, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; BBs, betablockers; CCBs, calcium channel blockers; CMD, coronary microcirculation dysfunction; CMR, cardiac magnetic resonance; DAPT, double antiplatelet therapy; PET, positron emission tomography; PFO, patent foramen ovale; SCAD, spontaneous coronary artery dissection; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. *The 3 diagnostic criteria for epicardial spasm on provocative test are: focal or diffuse epicardial coronary diameter reduction $\geq$ 90% in comparison with the relaxed state; nitroglycerine administration given to relieve the spasm; reproduction of the patient's symptoms and ischaemic ECG shifts. **The 2 diagnostic criteria for microvascular spasm on provocative test are: no epicardial vasospasm; typical ischaemic ST-segment changes and reproduction of the patient's symptoms.

follow-up for each type of MINOCA. Most importantly, the role of medical treatment in MINOCA still remains poorly understood as only observational studies are available. The current lack of RCTs might soon be mitigated by the results of the MINOCA-BAT trial, a randomized, parallel, open-label, multicenter trial with a 1:1:1:1 design, in which patients are randomized to either B-blockade alone, ACEI/ARB alone or a combination of B-blockade and ACE/ARB, or neither B-blockade nor ACEI/ARB. However, the inclusion of any type of MINOCA in this study represents a limitation that might result in unreliable results.[127] High expectations surround, instead, the PROMISE trial, a randomized, multicentric, prospective, trial, in which MINOCA patients are

Table 1 The table summarizes nine studies that evaluated the influence of beta blockers, statins, ACE inhibitors/ARBs, antiplatelet therapy and calcium channel blockers on the prognosis of MINOCA patients

Study	Study design	No. patients	MINOCA mechanism	Primary end point	SAPT (aspirin)	SAPT (P2Y12-I)	DAPT [a]	Beta blockers	Statins	ACEi/ARBs	CCBs
Manfrini *et al.* (2014)	Observational study	350	No	ALL-CAUSE DEATH OR (95% CI)	N/A	N/A	N/A	0.49 (0.10–2.08)	0.36 (0.05–2.38)	0.31 (0.03–0.78)	N/A
Lindhal *et al.* (2017)	Observational study	9136	No	MACE HR (95% CI)	N/A	N/A	0.90 (0.74–1.08)	0.86 (0.74–1.01)	**0.77 (0.68–0.87)**	0.82 (0.73–0.93)	N/A
Kovac *et al.* (2021)	Observational study	1986	No	MACE HR (95% CI)	1.02 (0.58–1.80)	N/A	N/A	1.09 (0.73–1.62)	**0.34 (0.23–0.51)**	0.51 (0.33–0.79)	0.63 (0.38–1.04)
Ciliberti *et al.* (2020)	Observational study	621	No	MACE HR (95% CI)	2.47 (1.05–5.78)	0.45 (0.22–1.68)	2.25 (0.58–8.79)	**0.49 (0.31–0.79)**	1.67 (0.91–3.05)	0.70 (0.40–2.21)	1.41 (0.77–2.5)
Paolisso *et al.* (2020)	Observational study	134	MRI ischemic pattern	MACE HR (95% CI) / ALL-CAUSE DEATH HR (95% CI) / RE-MI HR (95% CI)	0.80 (0.23–2.85) / 0.93 (0.20–4.33) / 0.56 (0.06–5.43)	0.82 (0.30–2.27) / 0.85 (0.26–2.78) / 0.73 (0.10–5.19)	0.42 (0.14–1.24) / 0.48 (0.14–1.64) / 0.28 (0.03–2.73)	0.43 (0.14–1.35) / 0.67 (0.14–3.09) / 0.17 (0.02–1.22)	0.44 (0.16–1.22) / 0.31 (0.09–1.01) / 1.26 (0.13–12.1)	**0.20 (0.06–0.70)** / **0.78 (0.08–7.99)** / 0.78 (0.08–7.99)	N/A / N/A / N/A
Bossard *et al.* (2021)	Observational study	1599	No	MACE HR (95% CI)	N/A	N/A	3.57 (1.31–9.76)	N/A	N/A	N/A	N/A
Montone *et al.* (2018)	Observational study	80	Evidence of vasospasm	ALL-CAUSE DEATH HR (95% CI)	N/A	N/A	N/A	N/A	N/A	N/A	2.72 (0.91–8.17)
Abdu *et al.* (2020)	Observational study	259	No	MACE OR (95% CI)	0.60 (0.31–1.18)	1.53 (0.78–3.01)	N/A	1.04 (0.55–1.99)	0.47 (0.24–0.91)	0.49 (0.24–0.99)	N/A
Choo *et al.* (2019)	Observational study	396	No	ALL-CAUSE DEATH HR (95% CI)	N/A	N/A	N/A	N/A	0.46 (0.22–0.96)	0.38 (0.16–0.92)	N/A

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channels blockers; DAPT, double antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiovascular events; N/A, not applicable; OR, odd ratio; P2Y12-I, P2Y12 inhibitors; re-MI, re-myocardial infarction; SAPT, single antiplatelet therapy. [a]Standard-dose or double-dose.

randomized 1:1 to a 'precision-medicine approach', consisting of a comprehensive diagnostic workup and pharmacological treatment specific for the underlying cause, versus a 'standard of care' approach, consisting of routine diagnostic workup and standard medical treatment for ACS. This trial should therefore clarify whether a treatment of MINOCA based on the identification of its mechanism leads to a significant improvement in prognosis compared with a general uniform treatment of these patients.[128]

Conclusion

MINOCA is an extremely heterogeneous clinical entity, including many possible scenarios with different pathogenetic mechanisms, diagnostic management, and therapy. It appears clear how a proper diagnostic workup is necessary to define the underlying cause and provide the most appropriate therapeutic strategy. This wide variety of possible causes justifies the lack of international guidelines and evidence-based therapeutic strategies, derived exclusively from observational studies (Table 1). It should be observed that the term MINOCA is in fact misleading, as it suggests that all patients receiving this diagnosis are similar and share the same prognostic and therapeutic approach. Accordingly, as stated above, the generic term of MINOCA should be avoided in the future, favoring, instead, terms that indicate the specific mechanism responsible for the occurrence of AMI in absence of obstructive CAD (see above).

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