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General Clinical Practice Update

Canadian Cardiovascular Society/Canadian Women's Heart Health Alliance Clinical Practice Update on Myocardial Infarction With No Obstructive Coronary Artery Disease (MINOCA)

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ABSTRACT

Myocardial infarction with no obstructive coronary artery disease (MINOCA) represents 6%-15% of all acute coronary syndromes, and women are disproportionately represented. MINOCA is an encompassing preliminary diagnosis, and emerging evidence supports a more expansive comprehensive diagnostic and therapeutic clinical approach. The current clinical practice update summarizes the latest evidence regarding the epidemiology, clinical presentation, and diagnostic evaluation of MINOCA. A cascaded approach to diagnostic workup is outlined for clinicians, for noninvasive and invasive diagnostic pathways, depending on clinical setting and local availability of diagnostic modalities. Evidence concerning the nonpharmacological and pharmacological treatment of MINOCA are presented and summarized according to underlying cause of MINOCA, with practical tips on the basis of expert opinion, outlining a real-life, evidence-based, comprehensive approach to management of this challenging condition.

RÉSUMÉ

L'infarctus du myocarde sans obstruction des artères coronaires (MINOCA) représente entre 6 et 15 % des syndromes coronariens aigus et touche nettement plus les femmes que les hommes. Le MINOCA est un diagnostic préliminaire général. Or, des données récentes militent en faveur d'une approche clinique diagnostique et thérapeutique plus large. La mise à jour actuelle de la pratique clinique résume les dernières données concernant l'épidémiologie, le tableau clinique et l'évaluation diagnostique du MINOCA. Une démarche diagnostique en cascade y est décrite à l'intention des cliniciens; celle-ci prévoit l'utilisation de procédures diagnostiques invasives ou non selon la situation clinique et les modalités diagnostiques accessibles à l'échelle locale. Les données se rapportant au traitement pharmacologique et non pharmacologique du MINOCA y sont présentées et résumées en fonction de la cause sous-jacente et s'accompagnent de conseils judicieux reposant sur l'avis d'experts pour opposer à cette maladie complexe une stratégie de prise en charge concrète, complète et factuelle.

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of interdisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

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Myocardial infarction (MI) with no obstructive coronary artery disease (MINOCA) represents 6%-15% of MIs.[1-6] MINOCA is a heterogenous and preliminary "umbrella" diagnosis. However, when thoroughly investigated, an underlying etiology can be identified in most cases.[7] A persistent gap in clinical outcomes is observed in women diagnosed with MI, including increased risk of in-hospital death, recurrent MI, and long-term mortality[8] with proportionately higher mortality rates after MI, particularly in younger women in Canada[9] who are also more likely to be diagnosed with MINOCA. Furthermore, trials concerning diagnostic testing have shown the utility of advanced cardiac imaging techniques including cardiac magnetic resonance imaging (CMR) and optical coherence tomography (OCT) in establishing underlying etiologies of MINOCA.[7] In MINOCA patients with plaque disruption or coronary vasospasm, tailored management approaches including secondary prevention and pharmacologic therapies have been associated with improved outcomes. Emerging evidence currently supports a more expansive comprehensive diagnostic and therapeutic clinical approach to MINOCA, highlighting the need for an up-to-date review and summary of recent data for today's cardiovascular clinician.

In the current document the epidemiology, clinical presentation, diagnostic workup, and treatment of underlying causes of MINOCA are summarized. Other international cardiovascular societies have previously published position statements on MINOCA.[10,11] In the present document data gathered through an updated systematic review are summarized, with a view from the perspective of unique aspects and challenges within the Canadian healthcare landscape.

Methods

A systematic review according to the **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) guidelines was conducted (Supplemental Fig. S1); the methodology is summarized in Supplemental Appendix S1. Identified literature through this review form the basis of this clinical practice update.

Definition

MINOCA is defined as MI (per the fourth Universal Definition of MI) without significant coronary artery stenosis (ie, > 50%) on coronary angiography.[11] The cutoff threshold of 50% diameter stenosis for defining "obstructive coronary artery disease" (CAD) in MINOCA is on the basis of historical studies that have evaluated coronary flow limitation in the presence of increasing degrees of stenosis.[12] In general terms, MI occurs because of obstruction of the blood supply to the myocardium, typically by a severe atherosclerotic stenosis, plaque disruption with thrombosis, intraluminal dissection, embolus, or vasospasm (macro or microvascular) causing local tissue death or apoptosis. In MINOCA, MI might occur because of these same mechanisms, however, the coronary arteries either appear normal or present luminal obstructions < 50% on coronary angiography.

MINOCA is thus comprised of a heterogenous group of cardiovascular disorders, including atherosclerotic and nonatherosclerotic conditions, which result in MI that is not due to obstructive CAD. It has become a term that is useful in grouping together diagnostic pathways when exploring the underlying pathophysiology of MI, in the absence of obstructive CAD. It is also important to make the distinction between MI and myocardial injury in the absence of obstructive CAD. For this reason, the definition of MINOCA also presumes that nonischemic causes of myocardial injury, like myocarditis or Takotsubo cardiomyopathy, have been excluded. It also requires that other forms of obstructive CAD have not been overlooked (Table 1). Notably, intraluminal spontaneous coronary artery dissection (SCAD) causing > 50% luminal obstruction is generally not considered to be MINOCA; however, sometimes SCAD can be a difficult angiographic diagnosis to establish, and "missed" diagnoses of SCAD might be labelled as MINOCA, until the specific diagnosis is established. In the absence of concomitant obstructive CAD, vasospasm causing MI is considered a cause of MINOCA, because of the transient nature of ischemic obstruction. MINOCA is distinct from ischemia with no obstructive CAD (INOCA), in that myocardial injury as evidenced by biomarker release is required to fulfill the definition of MINOCA, whereas cardiac biomarkers are normal in INOCA.

Epidemiology

Awareness of MINOCA has increased over the past few decades, especially with increasing utilization of high-sensitivity cardiac biomarkers with sex-specific interpretation thresholds,

Table 1. Diagnostic criteria for MINOCA

The diagnosis of MINOCA after coronary angiography for AMI-specific requirements:
1. Meets criteria for AMI, per fourth universal definition of myocardial infarction; detection of an increase and/or decrease in troponin level with at least 1 value > 99th percentile And at least 1 of the following: • Symptoms of myocardial ischemia • New ischemic ECG changes • Development of pathological Q waves • Imaging evidence of new loss of viable myocardium or new RWMA consistent with ischemic etiology • Identification of a coronary thrombus using angiography or in autopsy
2. No obstructive coronary artery disease (≥ 50% stenosis) in any epicardial artery or overlooked form of obstructive disease (spontaneous coronary artery dissection, embolus)
3. No clinically overt specific cause for the acute presentation (ie, myocarditis, Takotsubo cardiomyopathy)

AMI, acute myocardial infarction; ECG, electrocardiogram; MINOCA, myocardial infarction with no obstructive coronary artery disease; RWMA, regional wall motion abnormalities.

in the assessment of acute chest pain syndromes.[5,6] The reported incidence of MINOCA is variable, representing up to 15% of MIs, with the largest cohort studies reporting that MINOCA represents 6% of all MIs.[1-6,13,14] In the largest meta-analysis of 28 studies (median patient age 55 years; 40% female), a comparison of patients who presented with MI caused by obstructive CAD (MI-CAD) showed MINOCA patients to be younger, twice as likely to be female, and less likely to have hyperlipidemia, although other cardiovascular risk factors were similarly prevalent.[1] More recent studies have affirmed these findings, noting age, sex, and racial differences with the occurrence of MINOCA observed to be more common in younger individuals, women, and black patients.[5] In the **V**ariation **i**n Recovery: **R**ole of **G**ender on **O**utcomes of Young AMI Patients (VIRGO) study, MINOCA was seen in 1 of 8 women younger than the age of 55 years who had an acute MI, and these younger women had fivefold greater odds of MINOCA compared with young men who presented with an acute MI.[6]

Pathophysiology of MINOCA

Understanding the underlying pathophysiology of MINOCA is necessary to optimize clinical management. MINOCA can occur because of coronary plaque disruption, thromboembolism, vasospasm, microvascular dysfunction, or SCAD. MINOCA must also be distinguished from nonischemic "mimickers," such as myocarditis and stress-induced (Takotsubo) cardiomyopathy (Fig. 1).

Atherosclerotic causes account for approximately two-thirds of MINOCA, and most commonly include plaque disruption due to rupture, erosion, and calcific nodules, all of which can result in thrombus formation and distal thromboembolization.[10] In these patients, the pathophysiology and risk factor profile is similar to MI-CAD.

Nonatherosclerotic, coronary causes include epicardial coronary vasospasm, thromboembolism, SCAD, and coronary microvascular dysfunction (CMD).

Coronary vasospasm is a result of hyper-reactivity within the vascular smooth muscle, in the epicardial and/or microvascular vessels. Characterized by chest pain, transient electrocardiogram (ECG) changes, and responsive to nitroglycerin, coronary vasospasm can occur spontaneously or because of vascular smooth muscle hyper-reactivity in response to endogenous or exogenous allergens (Kounis syndrome),[15] drugs (ie, 5-fluorouracil), toxins (cocaine), or tumours (pheochromocytoma). In > 90% of cases, angiographic vasoconstriction can be demonstrated during provocative testing with acetylcholine or ergonovine.[16,17] Smoking is a risk factor for coronary vasospasm. Racial differences in vasomotor reactivity have also been described.[18]

SCAD is a unique nonatherosclerotic diagnosis occurring primarily (> 90%) in women, whereby a coronary intramural hematoma results in coronary luminal obstruction to distal flow. SCAD, an angiographic diagnosis with distinctive pathologic coronary artery features, is estimated to account for approximately 4% of all MIs. Further, SCAD accounts for approximately 40% of MIs in women aged younger than 50 years, and 14%-43% of pregnancy-related MIs.[19] However, a small percentage of SCAD cases might not be clearly recognized on the initial diagnostic coronary angiogram and additional imaging (OCT, intravascular ultrasound [IVUS]) might be necessary to assess for the presence of intramural hematoma - the angiographic hallmark of SCAD. Notably, these patients might be misclassified as having MINOCA until a definitive diagnosis of SCAD has been established. SCAD occurs in the presence of heterogeneous, multifactorial predisposing conditions and provocative factors, including fibromuscular dysplasia (25%-86% prevalence) and emotional or physical stress. However, inherited vasculopathies such as vascular Ehlers-Danlos syndrome and Marfan syndrome are infrequently reported (< 5%).[20]

Coronary thromboembolism is an uncommon cause of MINOCA occurring in < 3% of reported cases.[21] It can often affect the microcirculation and might not be seen on a diagnostic angiogram, resulting in underdiagnosis. Emboli can occur from thrombi formation within the coronary epicardial arteries, within systemic arteries, or within cardiac chambers or valves,[22] resulting from hereditary or acquired causes.[1,22]

CMD encompasses a spectrum of impaired nitric oxide-induced vasodilation, characterized by enhanced microvascular vasoconstriction, resulting in reduced myocardial blood flow reserve.[23-25] The prevalence of MINOCA cases attributable to CMD is uncertain.

Evidence on the precise etiologies of MINOCA is limited. The **H**eart **A**ttack **R**esearch **P**rogram (HARP) study, in which additional OCT or CMR testing was done in a cohort of 170 MINOCA patients, has provided some context for prevalence estimations of MINOCA etiologies.[7] OCT revealed a nonobstructive culprit lesion in 46% of patients, and plaque disruption was the most frequently identified cause, seen in 43% of the patients. However, only 59% of the patients underwent 3-vessel OCT, representing a limitation of the study.[7] In 3% of the cohort, thrombus without plaque disruption was diagnosed, 2% had evidence of coronary spasm, and 1 patient showed evidence of SCAD. Using CMR, 20% were identified to have a nonischemic cause, 53% were shown to have evidence of ischemia, and no cause was identified in 16%. Among patients who had OCT and CMR, 85% had an identified abnormality on one or both studies. Despite optimal workup, the cause of MINOCA remains undiagnosed in 8%-25% of cases.[7]

MINOCA does not include the diagnosis of type 2 MI,[10] which should be considered if there is a clear cause of supply-demand imbalance such as tachyarrhythmia, sepsis, anemia, or hypotension. The definition of MINOCA also does not include myocardial injury and subsequent infarction from nonischemic causes, such as Takotsubo syndrome and myocarditis, entities which also characteristically include no significant obstructive CAD at the time of angiography, and are thus termed MINOCA "mimickers."

Clinical Presentation

Patients with MINOCA usually present similarly to patients with MI-CAD, with symptoms characterized most often by acute chest discomfort or dyspnea, and elevated cardiac troponin level. These might be accompanied by ECG changes and new left ventricular regional wall motion abnormalities (RWMA). MINOCA occurs more frequently in the setting of a non-ST elevation MI compared with ST-elevation MI (STEMI).[26] MINOCA, by definition, requires

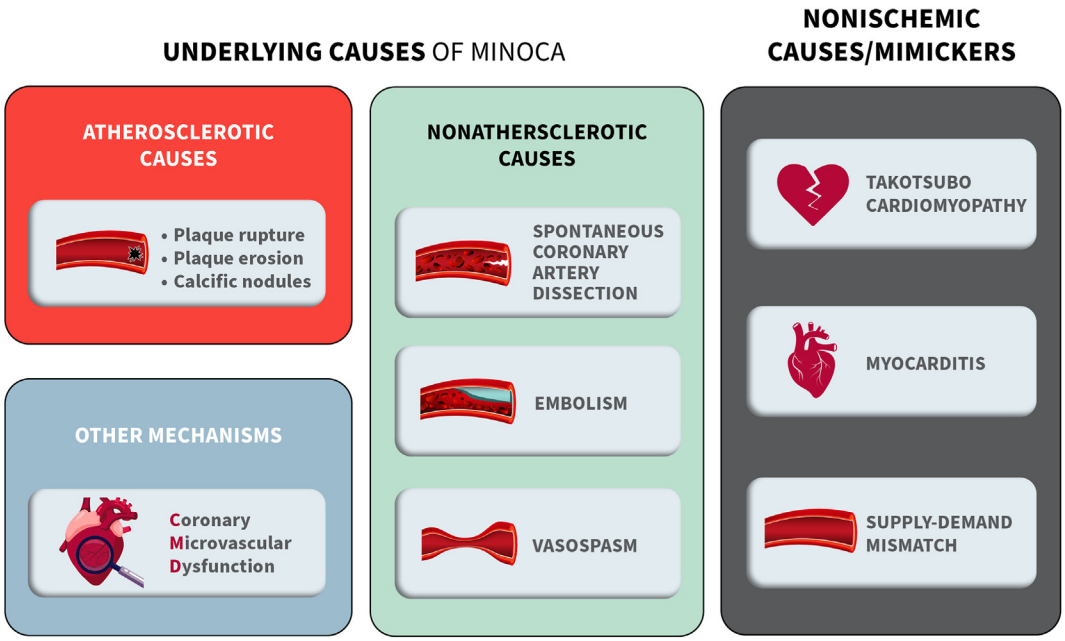

Figure 1. Underlying causes of myocardial infarction with no obstructive coronary artery disease (MINOCA).

coronary angiography to be established. Because of the similarities in clinical presentation, and the absence of obstructive CAD in Takotsubo cardiomyopathy and myocarditis, a careful clinical history and characteristic findings on noninvasive imaging will assist in differentiation.

Prognosis

The prognosis of patients who present with MINOCA is not benign. Reporting of mortality, major adverse cardiovascular events (MACEs), and readmission rates has been reported to be similar or lower, but not insignificant, for all age groups of patients with MINOCA compared with those with MI-CAD.[1,5,14] In a large single-centre contemporary analysis, the composite rate of mortality or nonfatal MI associated with MINOCA was more than twice that for patients without previous atherosclerotic cardiovascular disease (4.6% vs 2.2%), and compared with those with MI-CAD, it was approximately one-third (4.6% vs 14.3%).[2] CMR is of prognostic value in MINOCA patients, because findings can be used to stratify MACE outcomes according to CMR diagnoses of normal (3.5% 10-year MACE rate), acute myocardial infarction (47%), myocarditis (24%), or nonischemic cardiomyopathy (50%).[27] In a recent publication including 8560 consecutive STEMI patients, 5-year mortality hazard risk was 1.93 times higher in patients with MINOCA than those with MI-CAD; importantly, those with MINOCA mimicker diagnoses had outcomes similar to MI-CAD patients, emphasizing the need to diagnose underlying causes of MINOCA at the time of the event.[28]

Investigations and Diagnosis

The diagnostic pathway for MINOCA follows a cascade in which the clinician must progress through the following diagnostic steps: (1) make a working diagnosis of MINOCA by confirming universal criteria for MI are met, and that no coronary artery stenoses $>$ 50% are present; (2) carefully re-evaluate coronary angiography images (with or without adding intracoronary imaging in dubious cases) to ensure that SCAD or small branch occlusions are not present; (3) exclude mimic diagnoses such as Takotsubo cardiomyopathy or myocarditis; and then (4) attempt to identify the underlying pathophysiology of the MINOCA event. On the basis of this cascade principle, Figures 2 and 3, used together, show a proposed workflow algorithm to aid clinicians in establishing a MINOCA diagnosis and to identify the inciting pathological process. In developing this workflow algorithm, the panel sought to incorporate the key diagnostic steps while at the same time giving clinicians some degree of flexibility in choosing their preferred initial pathway (invasive vs noninvasive) on the basis of local availability of CMR and intracoronary imaging. As such, in some centres where CMR imaging can be done on a timely basis, clinicians may pursue an initial noninvasive pathway through CMR, then return to the catheterization lab for additional intracoronary imaging as a second step if still necessary. In other centres where intracoronary imaging can be done promptly and routinely, clinicians might prefer to start with the invasive diagnostic route, then use CMR as a second step when necessary. In some centres where neither CMR nor intracoronary imaging are easily accessible, temporary transfer to facilities with these diagnostic options might be necessary to complete the workup. The following sections outline the rationale and evidence for specific diagnostic tests in the pursuit of a MINOCA diagnosis and its pathophysiological etiology, while discerning first-line tests that should be considered in all patients from those that are supplementary in nature and might be used in selected situations.

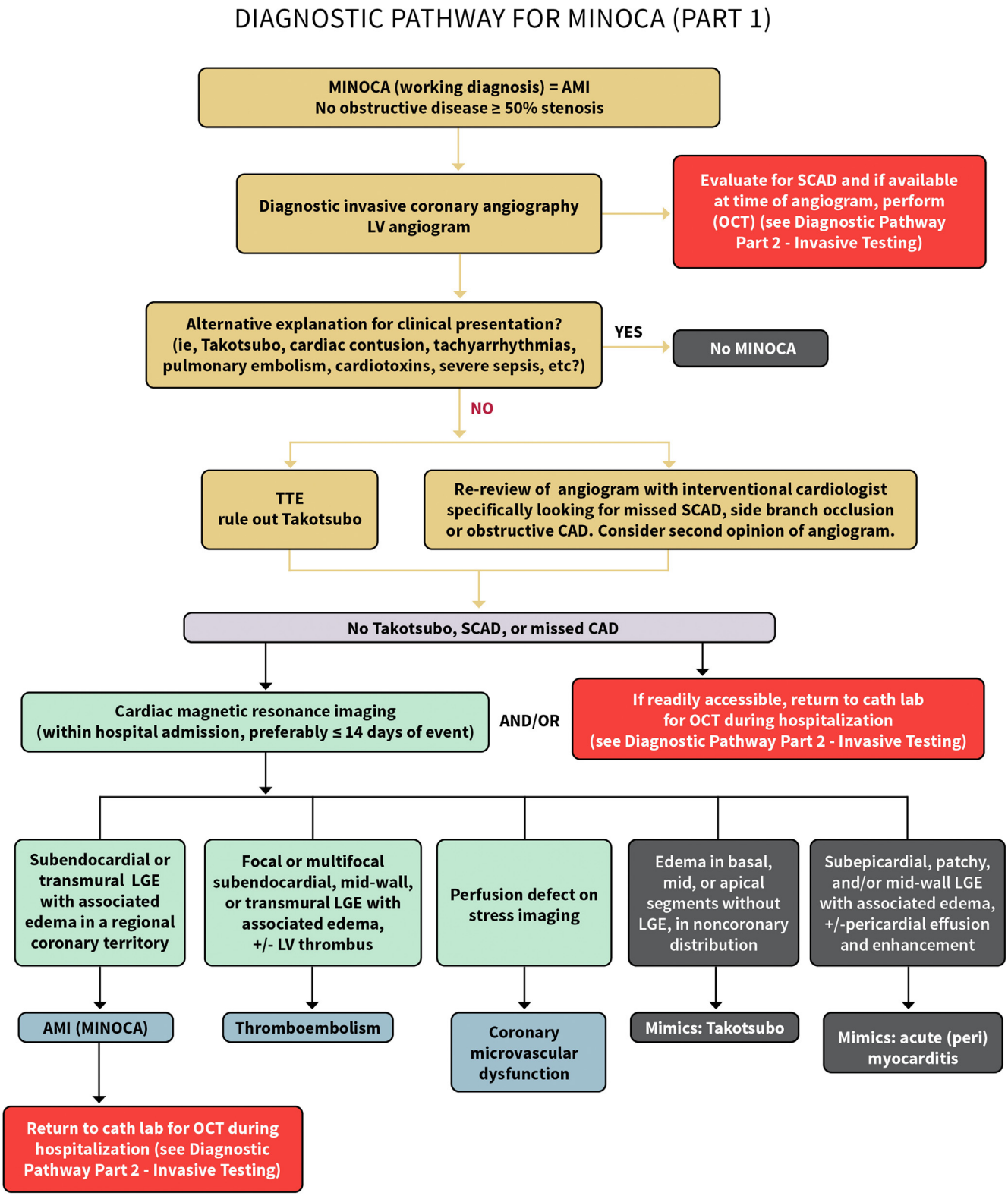

Figure 2. Diagnostic pathway for myocardial infarction with no obstructive coronary artery disease (MINOCA)—Part 1. AMI, acute myocardial infarction; CAD, coronary artery disease; cath lab, catheterization laboratory; LGE, late gadolinium enhancement; LV, left ventricular; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection; TTE, transthoracic echocardiogram.

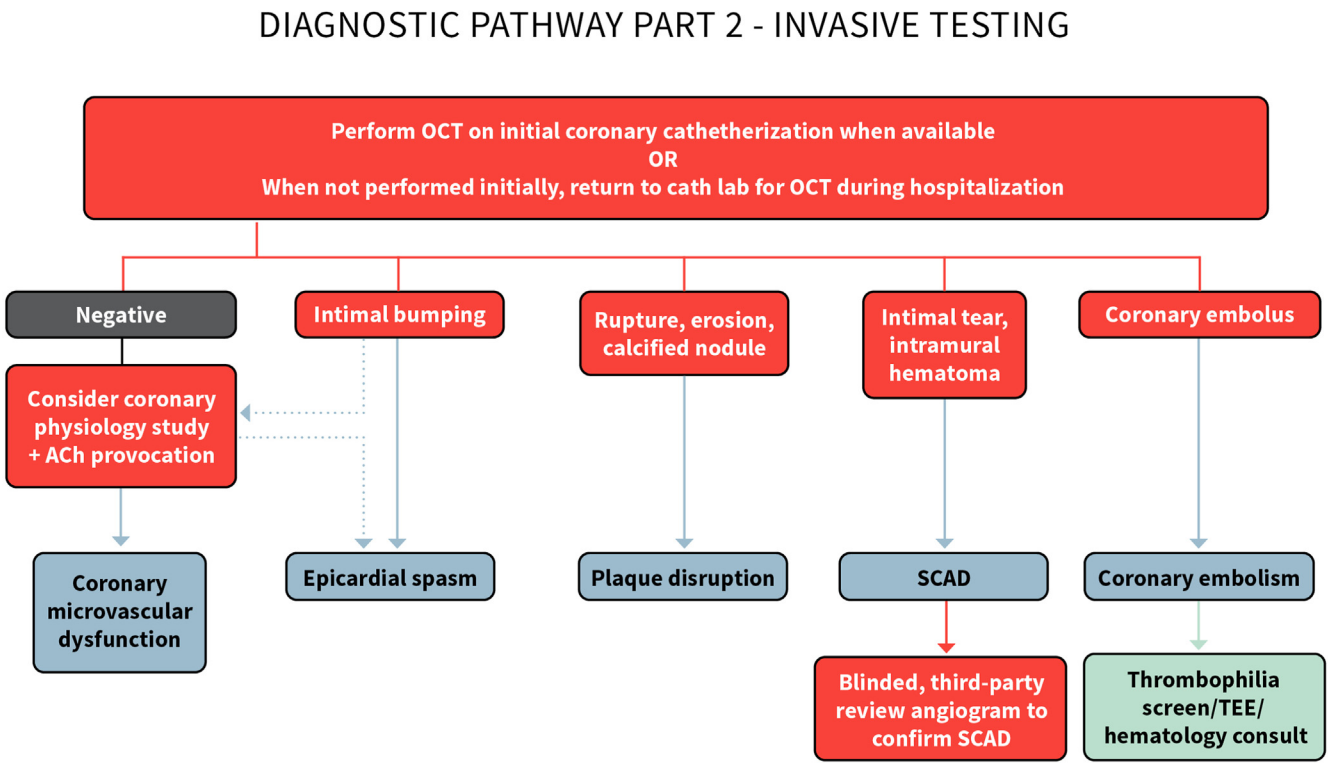

Figure 3. Diagnostic pathway for myocardial infarction with no obstructive coronary artery disease (MINOCA)—Part 2. ACh, acetylcholine; cath lab, catheterization laboratory; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection; TEE, transesophageal echocardiography.

Laboratory assays (first-line)

Troponin assessment, ideally with high-sensitivity assays interpreted according to sex-specific thresholds, is essential to the diagnosis of MINOCA. Additional laboratory testing is dependent on the clinical presentation. Conditions predisposing patients to a type 2 MI should be appropriately investigated. Routine bloodwork with a complete blood count is done to rule out anemia, inflammation (C-reactive protein), or infection. Additionally, when there is clinical suspicion, workup should include investigations for pulmonary embolism. If an embolic etiology is suspected, thrombophilia assessment should be additionally pursued.

Noninvasive imaging studies

Multimodality imaging plays an essential role in the evaluation and management of patients with MINOCA. Because of the heterogeneous etiologies, a combination of noninvasive imaging techniques not only helps to identify the underlying cause but can assess for other cardiac abnormalities that might guide tailored treatment strategies. The choice of imaging modalities depends on the clinical presentation, availability, and overall expertise of the medical centre. In many cases, a combination of techniques is necessary to reach a definitive diagnosis and guide appropriate management.

Transthoracic echocardiography (first-line). Transthoracic echocardiography (TTE) is essential in the workup of MINOCA and should be considered as the first imaging modality because of its widespread accessibility. We recommend its use in all patients who present with MINOCA to help confirm or refute alternative diagnoses, assess cardiac structure and function, and identify potentially coexisting conditions that might contribute to the clinical presentation.

TTE provides real-time evaluation of cardiac chamber size and function, left ventricular RWMA, valvular heart disease, and pericardial disease. Optimization of TTE with ultrasound enhancing (contrast) agents should be considered to aid in identification of RWMAs, and potentially assess myocardial perfusion for incremental information. A given RWMA, if present, could be in a regional epicardial coronary distribution that is supportive of MINOCA. Alternatively, RWMAs might be suggestive of Takotsubo cardiomyopathy, or indicate findings suggestive of underlying cardiomyopathy.[22] Additionally, echocardiography (including transesophageal, agitated saline, and/or commercially available contrast studies) can assist in the evaluation of suspected cardioembolic sources.[29]

Cardiovascular magnetic resonance imaging (first-line). CMR plays a central role in the workup of MINOCA[10,30] and has multiple strengths, including high-resolution cine imaging for visualization of subtle wall motion abnormalities not detected on TTE. Additionally, CMR has the capability of advanced tissue characterization, which can help with the diagnosis of acute MI vs MINOCA "mimickers." If locally

available, we recommend the use of CMR for all patients who present with MINOCA, when coronary causes such as plaque disruption and SCAD have been ruled out by the initial coronary angiogram and intravascular imaging (OCT, IVUS) as indicated and if available. CMR should be performed as soon as possible, within 1-14 days of presentation.[31] Even when performed after 2 weeks, CMR can help determine the underlying cause of MINOCA in at least 50% of patients.[31] When combined with OCT, multimodality imaging with CMR can identify a potential mechanism for MINOCA in approximately 85% of patients.[7]

CMR can be used to evaluate myocardial necrosis and fibrosis using late gadolinium enhancement (LGE), which can detect as little as 1 g of infarcted or injured myocardium.[32] LGE in a subendocardial or transmural pattern suggests an ischemic cause of injury and the regionality of the LGE can identify the culprit vascular territory in up to 99% of cases,[33]in addition to prognosticating adverse clinical events.[27] The presence of myocardial edema in a coronary distribution, detected using T2-based sequences, confirms the diagnosis of MINOCA. The presence of edema, usually in the absence of LGE with associated RWMA, suggests coronary vasospasm or Takotsubo cardiomyopathy.[34] However, depending on the severity of vasospasm, there might be subendocardial LGE, but provocative coronary physiology testing might be required for confirmation of vasospasm. CMD can be identified using CMR perfusion imaging, and can be associated with or without LGE/edema.[35] Multifocal regions of LGE might suggest coronary artery embolism,[36] and presence of left ventricular thrombus can also be assessed. A subepicardial appearance of LGE suggests nonischemic myocardial injury, and when coupled with findings of inflammation/edema using T1- and T2-based imaging, myocarditis can be diagnosed in approximately 30% of patients.[37]

Nuclear imaging (supplementary; case-based). Nuclear modalities, specifically positron emission tomography (PET), offer a highly accurate and reproducible means to evaluate myocardial blood flow, including myocardial flow reserve as a marker of coronary vasomotor dysfunction.[38,39] Although a myocardial flow reserve < 2.0 indicates a worse prognosis in the general population,[40] a specific cut point for CMD (as a cause for MINOCA) has not been established. In Canada, there is limited access to myocardial perfusion PET, which is available in a small number of tertiary care centres, limiting its broad application. Where it is available, PET imaging with myocardial blood flow quantification can be considered to diagnose CMD in patients with no obstructive coronary disease.[41]

Coronary computed tomography angiography (supplementary; case-based). Coronary computed tomography angiography can serve a supplementary role in the evaluation of MINOCA under specific conditions identifying plaque or myocardial bridging undetected by invasive angiography.[42] Although MINOCA is an invasive angiographic diagnosis, coronary computed tomography angiography is an alternative for patients who cannot or choose not to undergo invasive coronary angiography. The presence and extent of coronary atherosclerosis can be evaluated in situations in which the diagnosis of MINOCA is being considered; if presence of atherosclerosis is confirmed, secondary preventative therapies can be initiated.

Angiographic diagnosis

Coronary angiography is essential in the diagnostic workup of MINOCA, allows for the exclusion of significant coronary epicardial artery stenosis, and might reveal the cause of MINOCA. In addition, left ventriculography might help in the differentiation of coronary, noncoronary ischemic, or nonischemic mechanisms of myocardial injury. The presence and location of RWMAs can provide clues to the location of nonobstructive culprit lesions. This might prompt further intracoronary imaging, either OCT or IVUS, to interrogate those nonobstructive lesions.

If no obvious significant epicardial disease is seen, the coronary angiogram should be carefully reviewed for abrupt vessel occlusions or severe stenosis in small and distal vessels,[10,43] which might represent obstructive CAD, SCAD, coronary emboli, or thrombus. The angiogram should also be examined for subtle mild stenosis, especially in segments subtended by areas of wall motion abnormalities, to rule out SCAD or mild plaques with erosion/rupture/calcific nodules. Coronary functional testing should be considered for moderate lesions to ensure that they are not physiologically significant.[44]

Intracoronary imaging (first-line). Intracoronary imaging (IVUS and OCT) are useful to identify the cause of MINOCA, such as plaque erosion, plaque rupture, or calcific nodules,[45-48] and to rule out SCAD. The safety of intracoronary imaging in patients with acute coronary syndromes has been well established.[45,49] IVUS uses ultrasound to image the vessel wall and aid in the characterization of plaque composition, distribution, morphology, and extent. However, because of the very high frequency of the intracoronary catheters used, depth penetration and spatial resolution (200-250 μm) are limited, which affects assessment of fibrous cap thickness and plaque erosions. In a study of 42 MINOCA patients who underwent IVUS, 38% ($n = 16$) had plaque disruption with most of those having plaque rupture (29%, $n = 12$), whereas 10% ($n = 4$) had plaque ulceration.[48]

OCT is a light wave-based imaging technique which creates cross-sectional images of tissue with high resolution (10-15 μm).[50] It provides a detailed assessment of coronary plaque morphology, and the integrity and thickness of the fibrous cap.[51] OCT can identify plaque rupture, plaque erosion, calcific nodules, and thin-cap fibroatheroma (Fig. 4). Because of improved spatial resolution, plaque erosion is better identified on OCT compared with IVUS.[45] However, OCT has lower depth of field, and thus might not be suited for larger-sized vessels.[50]

In several cohort studies, OCT was used to identify the culprit in 46%-80% of MINOCA patients.[7,52,53] In a substudy of HARP, patients with MINOCA and MI-CAD were compared and thin-cap fibroatheroma (3% vs 35%), plaque rupture (14% vs 67%), plaque erosion (8% vs 14%), and calcific nodule (0 vs 6%) were less common in patients with MINOCA than in patients with MI due to obstructive CAD, whereas intraplaque hemorrhage (47% vs 2%) and layered plaque (31% vs 12%) were more common in MINOCA patients.[54]

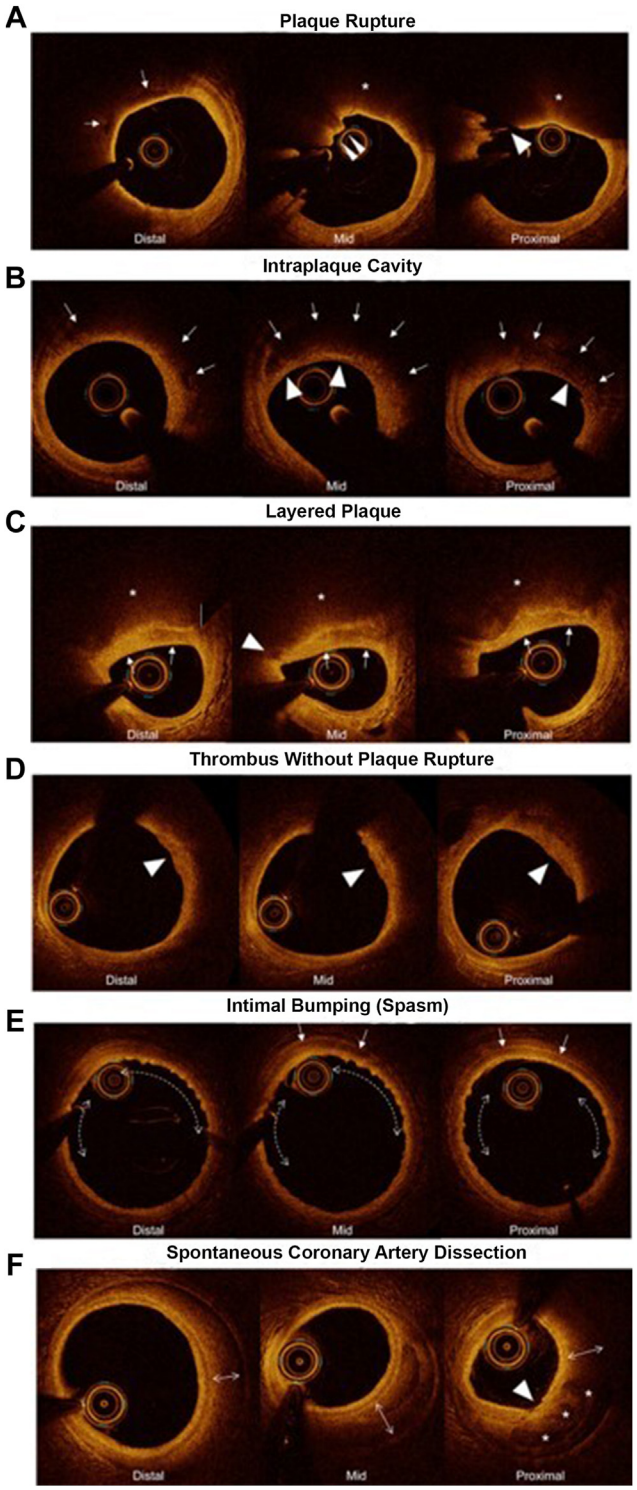

Figure 4. Identification of causes of myocardial infarction with no obstructive coronary artery disease (MINOCA) (< 50% stenosis in all major epicardial vessels) using optical coherence tomography. (**A**) Plaque rupture. In the proximal frame, there is discontinuity of a thin fibrous cap (**arrowhead**), indicating a plaque rupture, although it includes motion artifact. There is red thrombus superimposed on the rupture site in the mid frame (**narrow arrowheads**). In the distal frame, there are focal low-intensity regions indicating injected contrast within the ruptured cavity (**arrow**). The underlying plaque is a lipidic plaque (**asterisk**). (**B**) Intraplaque cavity. In the proximal, mid, and distal frames, there are low-intensity regions with limited attenuation indicating organized thrombus and/or injected contrast in the ruptured cavity (**arrows**) overlaying a high-backscattered fibrous cap (**arrowheads**). The fibrous cap (**arrowhead**) in the proximal frame looks thin, but there was no discontinuity of the fibrous cap, implying previous rupture with sealing. (**C**) Layered plaque. There is a heterogeneous layer (**arrows**) overlaying a lipidic plaque (**asterisk**) indicating healing of a recent plaque rupture event. In the mid frame, there is a focal low-intensity region (**arrowhead**) at the edge of the luminal interface of the layered plaque, indicating a potential site of previous rupture of the fibrous cap. (**D**) Mural thrombus without plaque rupture. There is a homogeneous region with irregular surface indicating platelet-rich mural thrombus (**arrowhead**). Within the underlying lipidic plaque, no clear rupture was observed. (**E**) Intimal bumping consistent with coronary artery spasm. Intimal bumping: there is diffuse intimal wrinkling (**dual-headed arrow**) along with thickening of the arterial media (**arrows**) indicating spasm. (**F**) Spontaneous coronary artery dissection. There is a dissection plane causing hematoma (**dual-headed arrow**) exterior to the arterial media, within the adventitia. There is an intimal tear (**arrowhead**, proximal frame) along with contrast flow into the false lumen (**asterisks**). Reproduced from Reynolds et al.[7] with permission from Wolters Kluwer Health, Inc. © 2020 American Heart Association, Inc.

Provocative physiologic testing (supplementary; case-based). Coronary provocative testing can be considered to diagnose epicardial coronary artery vasospasm and CMD. Vasospasm can be diagnosed by administering a stimulus (acetylcholine and/or ergonovine) during coronary angiography and monitoring for ischemic symptoms, ECG changes, and > 90% angiographic vasoconstriction. Microvascular vasospasm is defined by inducible chest pain, ischemic ECG changes, and < 90% angiographic vasoconstriction.[16] CMD can lead to abnormal blood flow response, impaired myocardial perfusion, and/or myocardial ischemia. It is defined as: impaired coronary flow reserve (< 2.0) in response to vasodilator stimuli such as adenosine, impaired microvascular blood flow measured according to corrected **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) frame count > 25 or abnormal coronary microvascular resistance (index of microvascular resistance > 25).[55] Although usually performed a few weeks after the acute event, small studies have shown the safety of performing testing within 48 hours of MINOCA diagnosis.[17] A study that included MINOCA and INOCA patients who underwent testing showed no difference in side effects (16% vs 14%; $P = 0.67$) or complications of provocative testing (1% vs 2.5%; $P = 0.44$).[56]

In a study of 80 patients with MINOCA who underwent provocative testing with acetylcholine (54%) or ergonovine (46%), almost half (46%) had an abnormal test, with epicardial spasm (in 65%) or microvascular spasm (in 35%).[17] Minor arrhythmias occurred in 5.4%, a rate comparable with that observed during spontaneous vasospastic angina attacks (7%), with no deaths or serious complications.[57]

In summary, coronary angiography is essential to the diagnosis of MINOCA, whereas ancillary invasive testing can assist in confirming the diagnosis and establishing the etiology of MINOCA.

Practical tips: MINOCA diagnosis

- Clinicians are encouraged to follow a cascaded approach in which the first step is to make a working diagnosis of

MINOCA; then exclude SCAD, small-branch coronary occlusions, and mimickers (ie, Takotsubo, myocarditis); and then chose a diagnostic path that best suits their clinical setting (early noninvasive path starting with CMR; or an early invasive path starting with intracoronary imaging).
- Echocardiography is uniformly recommended in all patients regardless of the diagnostic path chosen, because of its wide availability, low risk, relatively low cost, and significance of the information gained from this test (such as identification of RWMAs, or diagnosis of mimicker diagnoses such as Takotsubo or underlying cardiomyopathy).
- When an early noninvasive path is chosen, we recommend performing CMR within 1-14 days of presentation, and as early as possible, so as not to miss a potential diagnostic window for small infarcts, Takotsubo, or mild myocarditis.
- When an early invasive path is chosen, clinicians might adapt to the workflow of their catheterization laboratory to decide whether to perform intracoronary imaging at the time of index coronary angiography, or during a subsequent return to the catheterization lab after alternative diagnoses have been excluded.
- CMR and intracoronary imaging are considered first-line tests for MINOCA diagnosis. When CMR and intracoronary imaging (OCT) are performed, the etiology of MINOCA can be successfully identified in 85% of patients, which significantly aids in treatment and prognosis.
- Diagnostic tests such as cardiac PET, coronary computed tomography angiography, invasive coronary provocative testing, and thrombophilia workup are considered supplementary tests to be used on the basis of case-by-case indications.

Treatment of MINOCA

Values and preferences:

- The following approach to treatment of MINOCA (Fig. 5) is on the basis of expert opinion, because there are currently no available data from randomized clinical trials that have evaluated the efficacy of pharmacological secondary prevention therapy specifically in patients with MINOCA. Treatment of MINOCA according to specific causes are summarized in Table 2.

Nonpharmacologic treatment strategies

Referral to a cardiac rehabilitation (CR) program is a class I indication for patients with MI to optimize heart-healthy lifestyle and modify existing risk factors,[58,59] and its effect on physical and mental health might apply to MI-CAD and MINOCA patients.[60] Participation in CR is an independent predictor of favourable cardiovascular outcomes,[61] and one randomized controlled trial showed a significant reduction in all-cause mortality, MACE, and improvement peak oxygen consumption in 524 MINOCA patients.[62] There are also data to support benefits and safety of CR in the context of confirmed diagnoses of SCAD and CMD.[63,64] Finally, in patients who might have an allergic MINOCA precipitant, nonpharmacologic therapy includes avoidance of triggers.

Practical tips: Nonpharmacological treatment of MINOCA

- All patients with MINOCA should be referred to CR.
- Allergic precipitants of MINOCA should be avoided.

Pharmacologic treatment

Cause-specific treatment of MINOCA.

Coronary plaque disruption (or erosion). The treatment of MINOCA caused by plaque disruption or erosion will be similar to treatment of MI-CAD because of the common pathophysiology. Patients should be prescribed cardioprotective therapies, including aspirin, as suggested in the most recent guidelines.[10,11,65] Patients will also benefit from a $P2Y_{12}$ inhibitor, such as clopidogrel or ticagrelor.[11,66] The treatment should also include an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and a β-blocker.[11] Any patients with significant left ventricular dysfunction (ejection fraction $< 40\%$) and those with hypertension, diabetes mellitus, or stable chronic kidney disease should start treatment with an ACEI (Class I indication) or an ARB (Class IIa).[11,58,67] Statins are also indicated with the goal of reducing the low-density lipoprotein cholesterol by $> 50\%$ from baseline and achieving a level of < 1.8 mmol/L.[68]

Coronary microvascular dysfunction. There are no clinical studies of various therapies for CMD in the context of MINOCA. Small studies have examined pharmacologic management in patients with INOCA. Improvement in chest pain has been reported with first line antianginals such as β-blockers, calcium channel blockers (CCB) and to a lesser extent, nitrates.[69] Ranolazine, an antianginal medication now available in Canada, can be considered as second-line therapy.[70,71] Several studies have shown improvements in endothelial dysfunction markers, angina scores, coronary flow reserve, and exercise-induced ischemia with statins and ACEIs.[72-74] In the **Cor**onary **Mic**rovascular **A**ngina (CorMicA) study,[75] 151 patients with INOCA underwent CMD and provocative testing with adenosine and acetylcholine, and were randomized to medical therapy according to the testing results vs standard therapy (test results were blinded). The intervention group had improvement in angina and quality of life, but no difference in MACE at 6-month follow-up.[75]

Coronary vasospasm. The mainstay of therapy in patients with coronary vasospasm includes CCB[76] and nitrates.[77] A recent randomized clinical trial of 73 patients with invasive coronary flow testing showed a reduction in the prevalence of epicardial vasospasm with diltiazem treatment compared with placebo.[76] In patients with ongoing angina, dual CCB (non-dihydropyridine and dihydropyridine agents) may be considered.[78] Although nitrates are often acutely effective in relieving angina in patients with vasospasm, long-term issues such as nitrate tolerance limit their use.

In cases of refractory angina, nicorandil, a potassium channel activator that relaxes coronary vascular smooth muscle by stimulating guanylyl cyclase, increasing cyclic guanosine monophosphate levels, may be considered although it is

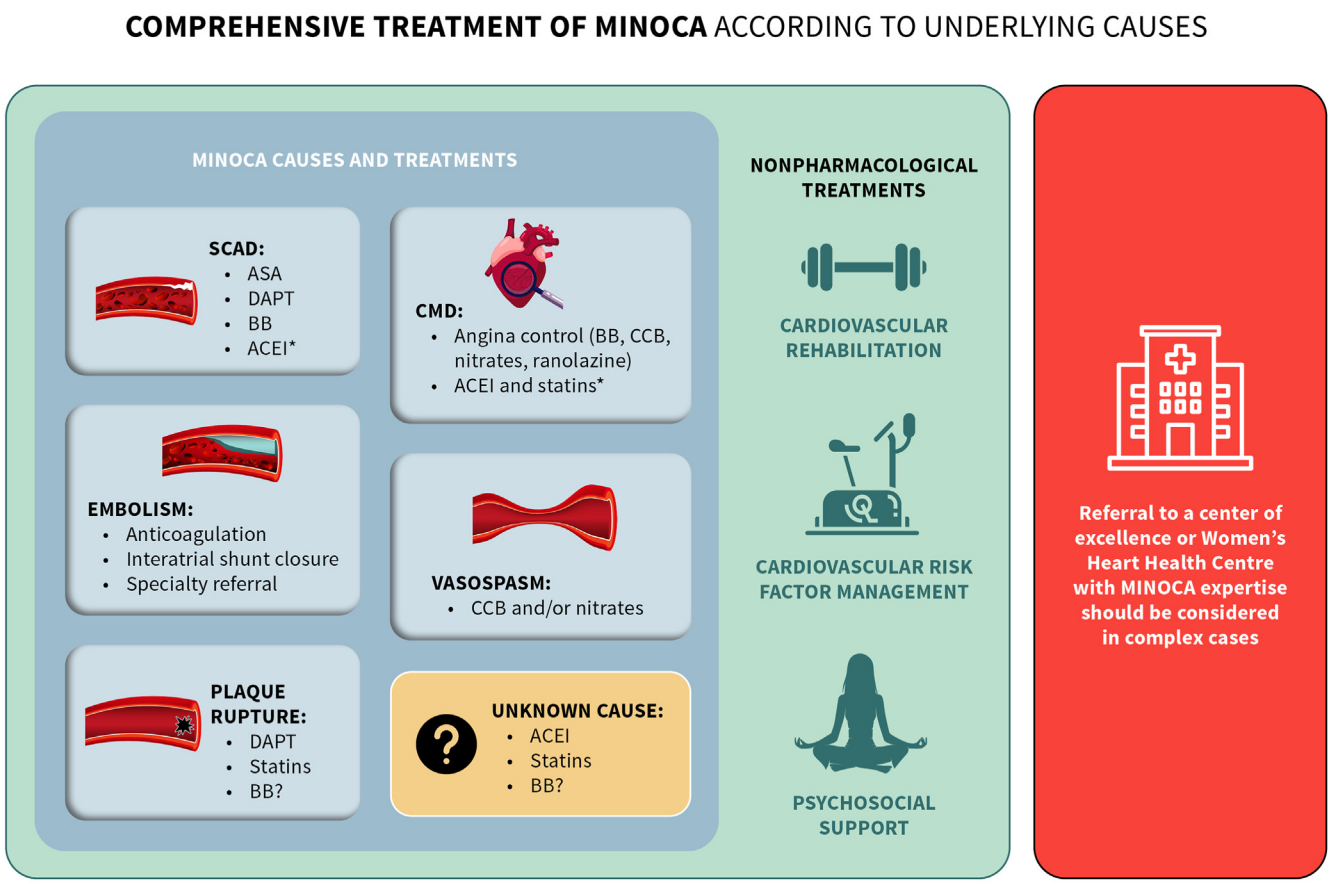

Figure 5. Comprehensive treatment of myocardial infarction with no obstructive coronary artery disease (MINOCA) according to underlying causes. ACEI, angiotensin-converting enzyme inhibitor; ASA, aspirin, BB, β-blocker; CCB, calcium-channel blocker; CMD, coronary microvascular dysfunction; DAPT, dual antiplatelet therapy; SCAD, spontaneous coronary artery dissection. *Consider if indicated for other conditions.

currently only available through the Health Canada special access program.[79,80] Aspirin has been shown in a retrospective study to reduce recurrent MI and chest pain in patients with a STEMI secondary to vasospasm.[81] However, a meta-analysis including data from 3661 patients with vasospastic angina showed no association between aspirin use and incidence of MI or cardiac death, but the proportion of patients with MINOCA was not specified.[82]

Spontaneous coronary artery dissection. There are currently no standard guidelines on the treatment of SCAD, because of a lack of randomized clinical trials.[83] In 70%-97% of cases in which follow-up angiography has been performed, there is angiographic evidence for spontaneous healing of SCAD,[84-87] and management aligns with the following important concepts.[88,89] Conservative medical therapy is recommended over acute revascularization, unless there is acute hemodynamic instability. Aspirin and β-blockers are the cornerstone of medical treatment.[89] In a large cohort study, β-blockers were associated with lower risk of recurrent SCAD (hazard ratio [HR], 0.39; 95% confidence interval [CI], 0.19-0.78; $P = 0.008$).[90] Patients who undergo percutaneous coronary intervention and stenting have a clear indication for dual antiplatelet therapy (DAPT).[64,91] However, for those treated medically, the benefit of DAPT remains uncertain, and might be a risk factor for increased bleeding.[92] However, because the intimal disruption in SCAD has a prothrombotic potential,[93,94] it was suggested that DAPT might have a protective effect and reduce the false lumen thrombus burden, which could theoretically reduce true lumen compression.[95,96] A common practice is to treat patients with lifelong aspirin, as well as clopidogrel for 3 to, at most, 12 months,[97,98] although these recommendations are variable, and must be modified according to side effects, including bleeding risk in young premenopausal women who experience menorrhagia with DAPT treatment; in these situations, low-dose aspirin alone is recommended.

In patients who present with SCAD, hypertension was reported to be a risk factor for recurrent disease (HR, 2.28 [95% CI, 1.14-4.55]; $P = 0.019$) and should be optimally managed.[90]

Early observations suggested that statins might be associated with a higher recurrence of SCAD,[99] however, this was not confirmed with later data. SCAD is a nonatherosclerotic process, and thus statins are not routinely indicated. Lipid-lowering therapy should only be prescribed to SCAD patients with a dyslipidemia indication, as per the most recent guidelines.[68]

Table 2. Summary of pharmacological treatment according to underlying cause of MINOCA

Underlying cause of MINOCA	Pharmacological agent(s)	Comments*
Plaque rupture	• DAPT • ACEI/ARB • Statins • β-Blockers	Recommended as per current guidelines regarding treatment of MI-CAD
SCAD	• Aspirin • β-Blockers	Should be strongly considered
Vasospasm	• CCB • Nitrates	Should be considered
Coronary microvascular dysfunction	• β-Blockers • CCB • Nitrates • Ranolazine • Statins	May be considered
Unknown underlying cause	• Aspirin • ACEI/ARB • Statins	May be considered

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; DAPT, dual antiplatelet platelet therapy; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with no obstructive coronary artery disease, SCAD, spontaneous coronary artery dissection.

*In the absence of definitive guidelines for MINOCA treatment, these suggestions are according to current clinical practice and expert opinion.

Coronary embolism. There are no data on the treatment of MINOCA due to coronary embolism. Anticoagulation is recommended in patients with atrial fibrillation,[100] suspected or diagnosed prosthetic valve thrombosis,[101] or intracardiac thrombus,[102] as per published guidelines. When an intracardiac shunt is shown and paradoxical embolism is clinically suspected, patent foramen ovale or atrial septal defect closure might be indicated.[103,104] As well, in cases in which thrombophilia is suspected, patients can be referred to a hematologist for further investigation and management.[105]

Practical tips: Cause-specific treatment of MINOCA

- MINOCA in the context of confirmed plaque disruption should be managed similarly to obstructive CAD.
- Antianginals including β-blockers, CCB, nitrates, and ranolazine should be considered for chest pain and quality of life in patients with MINOCA secondary to CMD. ACEIs and statins should be considered for CMD patients in whom there is already an indication.
- CCB (often dual pathway) and/or nitrates should be considered for patients with MINOCA from vasospasm.
- Aspirin and β-blockers are the mainstay medications for patients with SCAD and should be strongly considered.

Unknown underlying cause. In approximately 15% of cases, the exact underlying mechanism leading to MINOCA cannot be confirmed; therapy should be individualized according to optimization of cardiovascular risk profile and targeted treatment for probable underlying etiology.[7] Several observational studies have examined outcomes in patients with undifferentiated MINOCA with regard to use of mainstay post-MI therapies including ACEIs/ARBs, statins, β-blockers, and DAPT.[65,106-111] A recent meta-analysis pooled 10,546 MINOCA patients with 36 months of follow-up, and concluded that ACEI/ARB use was associated with reduced MACE (HR, 0.65; 95% CI, 0.44−0.94) but not all-cause death (HR, 0.48; 95% CI, 0.20-1.14).[112] In a Korean observational study ACEI vs ARB therapy was compared for secondary prevention in MINOCA patients, and no significant difference in outcomes were shown.[113] The most frequently reported cause of MINOCA is plaque disruption, for which statins are likely to provide benefit,[5-7] limiting progression and facilitating regression of atherosclerotic plaque,[114] in addition to favourable effects of statins on endothelial function, oxidative stress, and inflammation.[115,116] In large observational studies (sample size, n = 259-7512), statin use was significantly associated with a lower risk of MACE (HRs, 0.34-0.77)[65,108,109] and reduced risk of all-cause mortality in MINOCA patients.[65,110] A subgroup analysis of 5830 individuals from the **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies (SWEDEHEART) registry showed that reaching low-density cholesterol targets (< 2.5 mmol/L before 2012 and < 1.8 mmol/L thereafter) was independently associated with a 32% reduction of MACE.[61] Results from observational studies correlating the use of β-blockers with cardiovascular events in MINOCA have been inconsistent. Five observational studies reported a nonsignificant effect of β-blocker use on MACE and all-cause mortality.[106,108-111] In the SWEDEHEART registry (n = 7512), β-blockers showed a nonsignificant trend for reduced risk of MACE (HR, 0.86; 95% CI, 0.74-1.01), defined as all-cause mortality or hospitalization for MI, ischemic stroke, or heart failure.[65] The largest study to address antiplatelet therapy in patients with MINOCA was composed of a highly heterogenous population, including 66% of 9466 patients who received DAPT, and revealed a null effect of DAPT on MACE,[65] as shown in numerous other observational studies and post hoc analyses.[3,106-109,117] A recent meta-analysis showed that DAPT use in patients with MINOCA did not affect MACE or acute MI.[112]

Practical tips: MINOCA of unknown underlying cause

In patients diagnosed with MINOCA in whom a specific cause for MINOCA has not been identified:

- ACEI/ARB therapy should be considered in patients with MINOCA from plaque disruption or in whom an obvious other cause has not been identified.
- Statins should be considered in all patients in whom a specific cause has not been identified, considering potential event and mortality benefit with minimal risk.
- There is a lack of evidence to support the use of β-blockers in the absence of another indication.
- There is currently little evidence that supports the systematic use of DAPT in the context of MINOCA. The decision to use DAPT should be made in view of the most likely underlying diagnosis.

Centres of excellence

Diagnosis and treatment of MINOCA can be challenging because of local and regional limitations on access to specialized testing including such testing as OCT, IVUS, CMR, and coronary physiology reactivity testing. To assist in management and improve outcomes, referral to specialized centres should be considered in difficult to manage cases. Because MINOCA disproportionately affects women, specialized care for these patients (men and women) is most often provided in women's heart health centres or clinics, which currently exist in British Columbia, Ontario, Quebec, and Nova Scotia.[118] In a recent study in British Columbia the effect of enrollment in a women's heart centre with a focus on INOCA and MINOCA was examined, and significant improvements were observed in risk factor management, angina control, quality of life, and depression scores in addition to fewer emergency department visits and angina hospitalizations compared with pre-enrollment.[119]

Conclusions

MINOCA is a relatively common heterogeneous diagnosis which affects 6%-15% of all MIs, disproportionately affects women, and is likely underdiagnosed. To improve detection, outcomes, and quality of life for patients with chest pain and/or MI, clinicians must be aware of the diagnostic evaluation and treatment of MINOCA.

This Clinical Practice Update provides readers with up-to-date data, and is focused on 5 key areas: (1) what is MINOCA and how not to miss it; (2) the importance of excluding diagnostic "mimickers"; (3) flexible diagnostic pathways that are focused on laboratory testing and noninvasive and invasive imaging that can be adapted on the basis of each institution's availability and expertise; (4) the importance of understanding the underlying pathophysiology causing the MINOCA event to optimize treatment; and (5) the added benefit of post acute care resources, including referral to CR and centres of excellence, including women's cardiovascular health clinics or centres, especially if local expertise in MINOCA is not available.

Going forward, it is necessary to systematize timely diagnostic and treatment protocols for MINOCA at each institution to avoid underdiagnosis, followed by collection and publication of outcomes data to better understand the "state of affairs" of MINOCA in Canada. Furthermore, ongoing research is needed to refine diagnostic algorithms, and to establish randomized clinical trials aimed at the specific MINOCA population.

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Patient Consent

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2024.02.032.