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Myocardial infarction with non-obstructive coronary arteries (MINOCA)

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Myocardial infarction with non-obstructive coronary arteries (MINOCA) is evident in up to 15% of all acute myocardial infarctions (AMI) and disproportionately affects females. Despite younger age, female predominance, and fewer cardiovascular risk factors, MINOCA patients have a worse prognosis than patients without cardiovascular disease and a similar prognosis compared to patients with MI and obstructive coronary artery disease (CAD). MINOCA is a syndrome with a broad differential diagnosis that includes both ischemic [coronary artery plaque disruption, coronary vasospasm, coronary microvascular dysfunction, spontaneous coronary artery dissection (SCAD), and coronary embolism/thrombosis] and non-ischemic mechanisms (Takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy)—the latter called MINOCA mimickers. Therefore, a standardized approach that includes multimodality imaging, such as coronary intravascular imaging, cardiac magnetic resonance, and in selected cases, coronary reactivity testing, including provocation testing for coronary vasospasm, is necessary to determine underlying etiology and direct treatment. Herein, we review the prevalence, characteristics, prognosis, diagnosis, and treatment of MINOCA—a syndrome often overlooked.

KEYWORDS

myocardial infarction with non-obstructive coronary arteries, MINOCA, acute myocardial infarction, sex differences, coronary artery disease

Abbreviations: AMI, Acute myocardial infarction; CAD, Coronary artery disease; CFR, Coronary flow reserve; CMRI, Cardiac magnetic resonance imaging; IMR, Index of microvascular resistance; INOCA, Ischemia with no obstructive coronary arteries; IVUS, Intravascular angiography ultrasound; MI, Myocardial infarction; MINOCA, Myocardial infarction with non-obstructive coronary arteries; NSTEMI, Non-ST-elevation myocardial infarction; OCT, Optical coherence tomography; SCAD, Spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction.

Definition

Myocardial infarction (MI) without significant obstructive coronary artery disease (CAD) has been observed for decades in patients presenting with MI without a culprit artery. However, the term myocardial infarction with non-obstructive coronary arteries (MINOCA) was first introduced in 2013 (1), and it was not until 2017 that the European Society of Cardiology (ESC) position paper on MINOCA introduced diagnostic criteria for MINOCA based on the third universal definition of MI as follows: the presence of positive cardiac biomarker with clinical evidence of infarction, absence of stenosis ($\geq 50\%$) in any epicardial coronary arteries on coronary angiography, and lack of any alternative diagnosis for the index presentation (2). The underlying pathophysiologic mechanisms in MINOCA include: coronary artery plaque disruption, coronary vasospasm, coronary microvascular dysfunction, spontaneous coronary artery dissection (SCAD), coronary embolism/thrombosis, Takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy. In 2018, the universal definition of MI was updated to include only ischemic mechanisms associated with myocardial injury, thereby excluding non-ischemic mechanisms such as Takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy (3). Therefore, the American Heart Association (AHA) scientific statement in 2019 excluded non-ischemic mechanisms from the MINOCA definition and labeled them MINOCA mimickers (4).

Materials and methods

Electronic searches in MEDLINE were conducted through Aug 1, 2022, utilizing the following terms: MINOCA, plaque disruption, coronary vasospasm, coronary microvascular dysfunction, SCAD, coronary embolism/thrombosis, Takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy. All relevant retrospective and prospective observational studies and randomized clinical trials were considered without applying systemic inclusion or exclusion criteria. In addition, the reference lists of all relevant articles and reviews were manually searched.

Prevalence, clinical characteristics, and prognosis in MINOCA

Prevalence and clinical characteristics

MINOCA is considered a heterogeneous working diagnosis with an estimated prevalence of anywhere from 3 to 15% among all acute myocardial infarctions (AMI) patients (5–12). This heterogeneity is partly due to significant differences

in what conditions are included in the term MINOCA and which definition is used. In a pooled analysis of 23 studies, the prevalence of MINOCA was 8.1% among 806,851 consecutive AMI patients (12). MINOCA has been reported by large national registries worldwide, including the US, Japan, Poland, and Sweden, with the incidence of MINOCA ranging from 2.9 to 10.2% (6, 9, 13, 14). Compared to MI with obstructive CAD, MINOCA patients were younger, with a median age of ~ 61 years (12), and MINOCA was more common in Black (6, 8, 15) and Hispanic (16) patients. Further, MINOCA patients were less likely to present with traditional cardiovascular risk factors, including hypertension, dyslipidemia, diabetes, and current smoking history (12).

Prognosis in MINOCA

Given the low-risk profile and non-obstructive coronary arteries, MINOCA has historically been thought to be a benign disease process. However, compared to patients without known cardiovascular disease, MINOCA patients have consistently been reported to be at higher risk for cardiovascular events (7). For example, in a pooled analysis of three studies, in-hospital and 1-month all-cause death rates were significantly higher in MINOCA patients compared with people without known cardiovascular disease (adjusted OR: 25.4, 95% CI: 1.4–465, $p = 0.04$ and adjusted OR: 9.7, 95% CI: 1.6–58.7, $p = 0.03$, respectively) (12).

On the other hand, studies assessing the prognosis of MINOCA patients compared to those with obstructive CAD are conflicting due to differences in how MINOCA was defined (17). While some reported a worse prognosis in MI with obstructive CAD compared to MINOCA (6, 8), others reported a similar prognosis between patients with MI with obstructive CAD and MINOCA (5, 13, 16). For example, in a pooled analysis of fourteen studies, the unadjusted 1-year mortality rates were 3.4% in MINOCA patients, and 1-year reinfarction rates were 2.6% (12). Compared with obstructive CAD, MINOCA patients had significantly lower in-hospital and 1-year all-cause death rates (OR: 0.36, 95% CI: 0.2–0.5, $p < 0.001$ and OR: 0.60, 95% CI: 0.5–0.7, $P < 0.001$, respectively) (12). Whereas, a large retrospective study using a nationwide administrative database in Japan ($n = 137,678$) following the AHA 2019 scientific statement divided MINOCA patients into two groups: “true MINOCA” (those with underlying ischemic mechanisms, $n = 13,022$) and “working diagnosis of MINOCA” (those with underlying both ischemic and non-ischemic mechanisms, $n = 14,045$). The study suggested that regardless of the underlying mechanisms, both MINOCA groups were significantly associated with an increased risk of in-hospital death similar to patients with obstructive CAD (adjusted HR: 1.34, 95% CI: 1.21–1.48) and (adjusted HR: 1.34, 95% CI: 1.25–1.44), respectively (9).

Life-threatening ventricular arrhythmia and sudden cardiac death are not uncommon in patients with MI with obstructive CAD (18, 19). Similarly, myocardial ischemia, reperfusion injury, or inflammation around the scar tissue in MINOCA patients was hypothesized to precipitate ventricular arrhythmia (20). However, there has been little data to date on the incidence and prognosis of ventricular arrhythmia in patients with MINOCA. For example, in a small retrospective study of MINOCA and MINOCA mimicker patients with normal LV ejection fraction ($n = 131$), 18 developed ventricular arrhythmias during the index hospitalization, but none had sudden cardiac death (21). On the other hand, in a prospective study of young MINOCA patients, only 4 out of 299 had a cardiac arrest at presentation and had an automatic implantable cardioverter-defibrillator (16). In addition, no previous research has investigated supraventricular arrhythmia in MINOCA patients. Therefore, future studies are warranted to determine the incidence and prognosis of arrhythmias in MINOCA patients.

ST-elevation MINOCA compared with non-ST-elevation MINOCA

The majority of MINOCA patients (70–80%) present with non-ST-elevation myocardial infarction (NSTEMI), limiting our understanding of ST-elevation myocardial infarction (STEMI) in MINOCA patients (12). ST-segment elevation at presentation is a predictor of all-cause death in MINOCA (5). And patients with STEMI have been shown to have a higher risk of mortality than those with NSTEMI (22, 23). However, studies investigating STEMI MINOCA are quite limited. A single-center, retrospective study of STEMI patients undergoing coronary angiography in the UK ($n = 2,521$) reported that only 4.4% of the study population had MINOCA, based on the ESC 2017 criteria. All-cause mortality rates were 3.6% in 30-day and 4.5% at 1-year follow-up (24). More recently, a single-center prospective registry in Denmark ($n = 4,793$) reported that 11% of STEMI activations had normal (0% stenosis) or non-obstructive (1–49%) coronary arteries but only 6.5% ($n = 310$) had elevated cardiac troponin. In a multivariable analysis, long-term mortality risk was twofold higher in patients with normal coronary arteries and elevated cardiac troponin than those with obstructive CAD (HR: 2.65, 95% CI: 1.52–4.61, $p = 0.001$) (25). To our knowledge, no studies to date have evaluated the difference in pathophysiologic mechanisms in NSTEMI vs. STEMI MINOCA, emphasizing the need for further research.

The role of sex in MINOCA

MINOCA disproportionately affects females (26). Recent meta-analyses demonstrate that females comprise up to 50%

of MINOCA patients (11, 12). Analysis of young patients with AMI in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) showed that females had about five times higher odds of having MINOCA than males (14.9 vs. 3.5%, OR: 4.84, 95% CI: 3.29–7.13) (16). In the same study, 269 females had MINOCA, and the majority had MINOCA undefined (75%), 4% spasm, 21% dissection, and 1% embolization (16). The Heart Attack Research Program-Imaging Study (HARP), a study of females presenting with MINOCA primarily composed of NSTEMI, reported that plaque disruption was the most common cause of MINOCA (27).

Given the limited data, it remains unclear whether sex disparities in obstructive CAD are also evident in MINOCA. For example, in a small, single-center, prospective study of MINOCA patients, females were older and more likely to have a higher cardiovascular risk profile. However, the long-term prognosis was comparable in males and females (28). On the other hand, an analysis of MINOCA patients from ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines) showed a higher incidence of in-hospital MACE (a composite of death, reinfarction, cardiogenic shock, or heart failure) in females than males (5.4 vs. 4.1%; $p < 0.0001$) (8).

Although data on sex differences in MINOCA patients are limited, several studies have explored it in subtypes of MINOCA and MINOCA mimicker, i.e., SCAD and Takotsubo cardiomyopathy. SCAD disproportionately affects females (~90%), particularly young females (29, 30). Although the underlying biological basis remains determined, pregnancy and hormonal replacement therapy are associated with a higher risk of SCAD in females (31). Pregnancy-associated SCAD is the most common cause of MI during pregnancy (32) and occurs predominantly during the third trimester and early postpartum (33). Notably, females with pregnancy-associated SCAD were more likely to present with high-risk cardiovascular features at presentation than females with SCAD outside of pregnancy (34). Sex disparities in SCAD, however, are poorly described. In a single-center, prospective cohort study of patients with SCAD ($n = 288$), only 8.7% were males; compared to females, males were younger, more likely to perform isometric exercise preceding SCAD, and less likely to have emotional stressors (35). There was no sex difference in long-term cardiovascular events (35). In terms of angiographic characteristics, a single-center, retrospective observational study reported that males were more likely to have type 1 SCAD and intimal tear than females (36).

Similarly, Takotsubo cardiomyopathy disproportionately affects females, particularly postmenopausal females, (37) sex differences have been reported. For instance, males are younger (38) and more likely to have physical stressors preceding Takotsubo cardiomyopathy (39), whereas females are older (38) and more likely to have emotional

stressors preceding Takotsubo cardiomyopathy (39). In addition, the male sex was an independent predictor of short and long-term mortality risks in patients with Takotsubo cardiomyopathy (40, 41). In accordance with prior studies, a recent large multicenter registry-based cohort of patients with Takotsubo cardiomyopathy ($n = 2,492$), including 11% of males, reported males were younger but had a high prevalence of cardiovascular risk factors. In multivariable adjustment, the male sex increased in-hospital mortality risk by more than twofold and long-term mortality risk by more than 80% (42).

Underlying pathophysiologic mechanisms in MINOCA

The underlying pathophysiologic mechanisms in MINOCA include: coronary artery plaque disruption, coronary vasospasm, SCAD, coronary embolism/thrombosis, MINOCA-mimickers (Takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy), and coronary microvascular dysfunction (Figure 1).

Plaque disruption

Plaque disruption is an umbrella term that includes plaque rupture, erosion, and calcified nodules. As lipids accumulate in coronary arteries, the surge in inflammation, necrosis, fibrosis, and calcification leads to plaque formation, which may progress and be complicated by disruption (43). Plaque rupture results in the exposure of the plaque to the coronary lumen, which results in thrombosis and thromboembolism (44), while plaque erosion results from thrombus formation adjacent to the luminal surface following endothelial cell apoptosis and neutrophils' recruitment without rupture (45). Female sex and smoking history are associated with an increased risk of plaque erosion compared to rupture (46). Plaque rupture can be detected utilizing intravascular imaging including intravascular angiography ultrasound (IVUS) or coronary optical coherence tomography (OCT); whereas the higher resolution of OCT is needed to assess plaque erosion (47). In a multi-center prospective study, plaque rupture (and ulceration) existed in 38% of females with MINOCA ($n = 16/42$) who underwent IVUS (48). The HARP study reported that plaque disruption was the most common cause of MINOCA, as was evident in 43.4% of females with MINOCA who underwent OCT including 8 with plaque rupture, 5 with plaque erosion, and the rest had an intra-plaque cavity or layered plaque (27). Notably, only 59% of participants had three-vessel OCT, which may have led to an underestimation of the prevalence of plaque disruption (27).

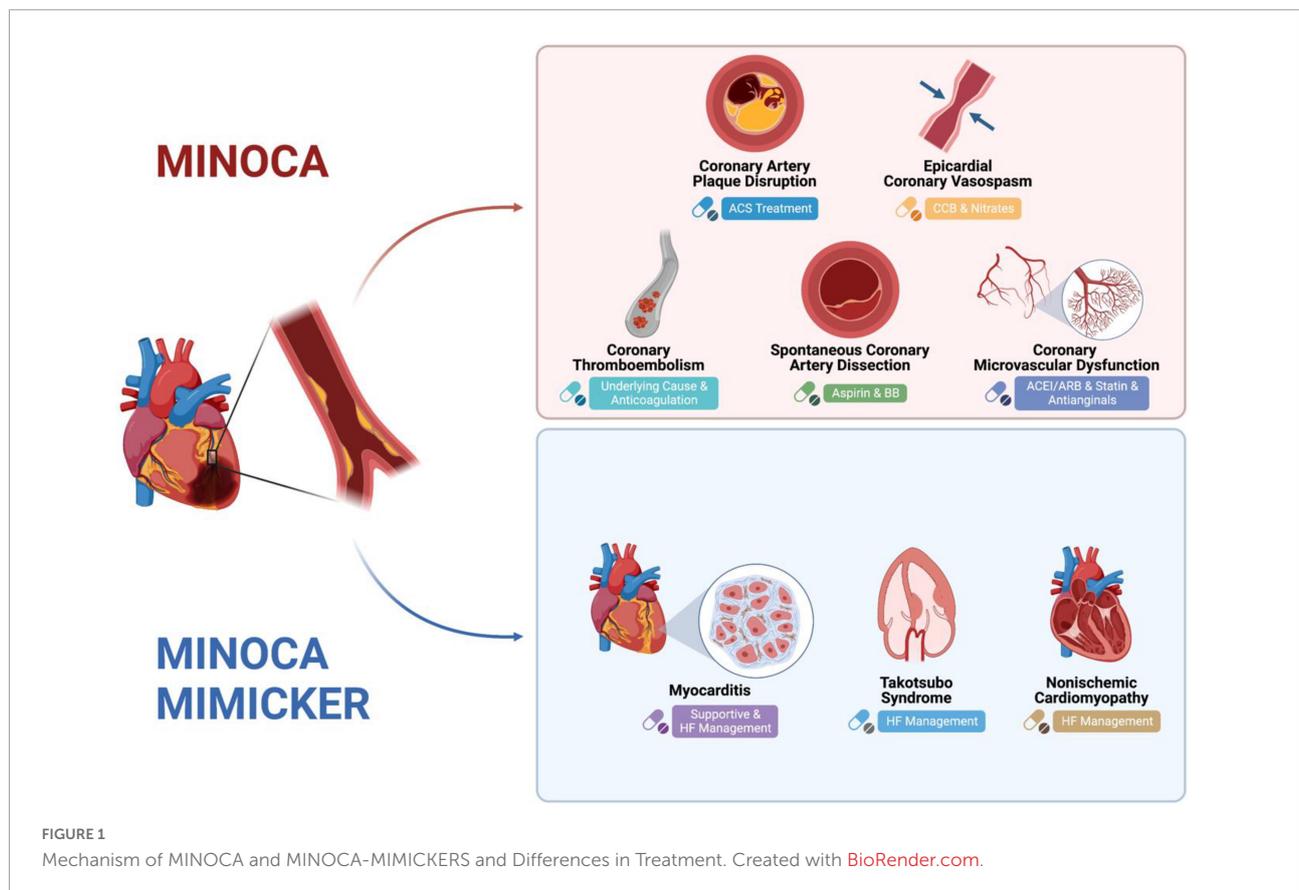
Coronary vasospasm

Coronary vasospasm is defined as reproducible nitrate-responsive chest pain with transient ischemic EKG changes and >90% vasoconstriction on angiography in provocative testing with acetylcholine or ergonovine (49). The predominant pathophysiological mechanism is hyper-reactivity within the vascular smooth muscle in either the epicardial or microvascular vessels (50). Coronary vasospasm is a common cause of MINOCA, with about half of MINOCA patients having a positive provocative test in a single-center prospective study (51). Asians are at increased risk of coronary vasospasm with up to threefold higher risk of acetylcholine-provoked coronary vasospasm than Whites (52). Smoking is a known risk factor for coronary vasospasm (53). In contrast, other traditional risk factors such as sex, hypertension, diabetes mellitus, or hyperlipidemia were unrelated to increased coronary vasospasm risk (54). Coronary vasospasm is associated with a 2.5–13% long-term risk of MACE (55).

Spontaneous coronary artery dissection

SCAD results from the formation of a false lumen within the wall of epicardial coronary arteries in the absence of atherosclerosis (31). Two potential pathological mechanisms have been described, including an inside-out model where a tear in the intima layer resulting in a false lumen and an outside-in model where the formation of a false lumen following a spontaneous intramural hemorrhage with or without an intimal tear (31). Based on angiographic characteristics, four types of SCADs have been described: type 1 describes multiple radiolucent lumens and staining within the arterial wall, type 2 describes diffuse and smooth stenosis, type 3 describes focal stenosis mimicking atherosclerosis, and type 4 describes total vessel occlusion (29, 30). Although coronary angiography has limitations, it remains the principal diagnostic tool for SCAD (29, 30). In cases of diagnostic uncertainty or need for any invasive intervention, advanced intracoronary imaging modalities, IVUS or OCT, may be considered with caution, given the risk of propagating the dissection (29, 30).

The true prevalence of SCAD is unknown, given that the diagnosis is often missed. In the largest study of STEMI, SCAD was evident in only 1% of STEMI patients and was more prevalent in females (93%) (56). SCAD that results in a non-obstructive lesion or is missed at initial presentation is considered MINOCA as recommended by the AHA statement, whereas SCAD that results in complete vessel occlusion (type 4) is excluded (4). The predisposing mechanisms for SCAD are multifactorial, including genetic factors, fibromuscular dysplasia, pregnancy, female sex hormones, systemic inflammatory condition, and precipitating factors



such as emotional stress, rigorous physical activity, or stimulant drugs (29, 30).

Coronary embolism/thrombosis

Coronary embolism is often underdiagnosed and understudied. The type of coronary embolism is dependent on the thrombus origin: direct (from the left atrium, left ventricle, or valvular origin), paradoxical (from the venous circulation to systemic circulation through septal defects), or iatrogenic (from intracoronary or valvular interventions) (57). A retrospective analysis of a national database in Japan revealed that only 2.9% of all AMI patients had a coronary embolism, of which 73% were secondary to atrial fibrillation (58). During a median follow-up of 49 months, 1 out of 10 patients with coronary embolism developed recurrent thromboembolic episodes despite most patients having a CHADS2 score of 0 or 1 (58). Certain conditions, such as hereditary or acquired thrombophilia, increase the risk of coronary thromboembolism. In a meta-analysis of eight studies of MINOCA with available thrombophilia screening data, 14% had hereditary thrombophilia, with Factor V Leiden as the most common (11). Therefore, an extensive evaluation, including hypercoagulable workup, monitoring for atrial fibrillation, and

assessment for patent foramen ovale, is needed to determine the underlying causes of coronary embolism (59).

MINOCA mimickers

Takotsubo cardiomyopathy, also commonly referred to as stress-induced cardiomyopathy or broken heart syndrome, is characterized by reversible wall motion abnormalities without obstructive CAD due to a surge of catecholamines (60). Four major anatomical variants are observed: apical ballooning (most common), mid-left ventricular, basal, and biventricular (61). Clinical presentations vary but often follow emotional or physical stress, such as critical illness (62). Takotsubo cardiomyopathy is more prevalent in females, especially those postmenopausal females (63). Several studies suggested that coronary artery vasospasm and microvascular dysfunction may be part of the pathophysiologic mechanism (64). Diagnosis is often made with coronary angiography demonstrating an absence of obstructive CAD and characteristic wall motion abnormality on the left ventriculogram and evidence of complete recovery of left ventricular function and wall motion abnormality on followed-up transthoracic echocardiogram (62). Cardiac magnetic resonance imaging (CMRI) is a useful tool in Takotsubo cardiomyopathy to exclude other causes of AMI (63).

Although Takotsubo cardiomyopathy is reversible, cardiogenic shock and death risks are comparable to AMI patients with CAD in several observational cohorts (65–67).

Myocarditis or inflammatory cardiomyopathy is commonly caused by viral infections, but it can also be caused by bacterial infections, toxic substances, or autoimmune disorders (68). Myocarditis is more common in younger patients, although it affects patients of all ages. Fulminant myocarditis, although rare, can result in life-threatening cardiogenic shock (69). Diagnosis of myocarditis is made using CMRI characterized by the presence of diffuse myocardial edema on T2 and with myocardial biopsy (70, 71). In a meta-analysis of five observational studies with available CMRI data, one-third of MINOCA patients had myocarditis. It was more common in younger patients and those with high C-reactive protein (72).

Non-ischemic cardiomyopathy includes dilated cardiomyopathy (most common), hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic cardiomyopathy (73). A longitudinal observational study assessing the prognostic role of CMRI in MINOCA patients revealed that 25% of the participants had MINOCA due to non-ischemic cardiomyopathy. Further, non-ischemic cardiomyopathy was associated with the highest mortality compared to other mechanisms of MINOCA (74). Using stress CMRI, underlying microvascular dysfunction has been reported in patients with dilated cardiomyopathy (75).

Coronary microvascular dysfunction

It remains debatable whether microvascular dysfunction is among the causes of MINOCA, given the lack of data to date. Coronary microvascular dysfunction stems from impaired vasodilation, increased vasoconstriction, and abnormal remodeling of microcirculation, which alters the coronary flow reserve (CFR) in the absence of epicardial obstructive disease (76). Coronary microvascular dysfunction is often underdiagnosed because it requires invasive functional tests (77). The majority of studies assessing coronary microvascular dysfunction have been completed among patients with ischemia with no obstructive coronary arteries (INOCA), with a prevalence of up to 41% (78). However, in a small prospective study of MINOCA patients ($n = 40$) who underwent stress CMRI, 25% had low myocardial perfusion reserve index (≤ 1.84), without evidence of late gadolinium enhancement on CMRI or plaque disruption on IVUS (79). Further research is needed to determine if microvascular dysfunction is one of the causes of MINOCA.

Diagnostic modalities for MINOCA

MINOCA is a syndrome, not a diagnosis, requiring a comprehensive diagnostic workup. Coronary angiography

is the first-line diagnostic tool to detect non-obstructive epicardial coronary arteries (<50% stenosis) in the setting of an MI. Although its role is limited to identifying the underlying mechanisms, it may offer leading insights; such as evidence of haziness or filling defect in plaque disruption, fresh thrombosis with the reduced distal flow in coronary embolism/thrombosis, evidence of false lumen in SCAD, and evidence of apical ballooning on the left ventricular angiogram in Takotsubo cardiomyopathy (4). Therefore, advanced imaging modalities are vital in diagnosing and identifying the underlying mechanisms of MINOCA (80).

Coronary intravascular imaging

Coronary intravascular imaging with IVUS and OCT is essential in evaluating MINOCA to diagnose plaque disruption. It should be performed at the time of coronary angiography for AMI in all 3 major epicardial arteries. In MINOCA patients, IVUS detected plaque disruption in up to 40% of cases (48) and OCT detected the underlying culprit lesion in about half of cases (27). Intravascular imaging can also be useful in the evaluation of SCAD in selected cases where diagnosis is uncertain.

Cardiac imaging

Transthoracic echocardiography is useful in the assessment of cardiac function after a MINOCA event. It can be used in the diagnosis of takotsubo cardiomyopathy and non-ischemic cardiomyopathy and is particularly helpful in follow-up to demonstrate recovery of left ventricular function (81). In addition, transesophageal echocardiography might be considered in the workup when coronary embolism is suspected (82).

CMRI is recommended by the ESC guidelines in all MINOCA cases where a diagnosis is uncertain (2). CMRI provides an appropriate diagnosis in 74–87% of all MINOCA patients (74, 83–87). CMRI subendocardial (or transmural) pattern of myocardial edema, inflammation, or fibrosis is suggestive of ischemic MI, whereas an epicardial pattern is suggestive of non-ischemic MI (81). Native T1 and extracellular volume mapping detect areas of fibrosis and edema that, in a vascular pattern, are suggestive of MI even in the absence of late gadolinium enhancement. Further, CMRI, like an echocardiogram, can be used to diagnose takotsubo cardiomyopathy and non-ischemic cardiomyopathy, but CMRI is the only imaging modality that can be used to diagnose myocarditis. In addition, myocardial perfusion quantification with adenosine or regadenoson can be used to diagnose coronary microvascular dysfunction non-invasively (88). Newer technologies such as high-resolution late gadolinium enhancement CMRI, using a 3-dimensional respiratory-navigated method, modified about half of the uncertain

diagnoses (48%) in MINOCA patients, where transthoracic echocardiography, ventriculography, and conventional CMRI were non-diagnostic (89).

The timing of CMRI from the time of the event is critically important, and CMRI is recommended to be completed as close to the AMI as possible. The diagnostic performance of CMRI increased significantly from 47% when performed at a median of 12 days to 77% when performed at a median of 3 days after hospital admission (87). CMRI also carries not only diagnostic but also prognostic value. CMRI confirmed MI was an independent predictor of long-term cardiovascular events (86).

Invasive functional studies

Provocative spasm testing using acetylcholine or ergonovine (no longer available in the US) is used to diagnose coronary epicardial or microvascular vasospasm and endothelial-dependent coronary microvascular dysfunction (90). Provocative spasm testing is performed with the administration of intracoronary acetylcholine. A recent meta-analysis of studies assessing procedural complications of intracoronary acetylcholine was encouraging as the overall incidence of complications following intracoronary acetylcholine was only 0.5%, without any incidence of death (91). Moreover, there was no significant change in safety and diagnostic yield between administering 100 vs. 200 μ g of intracoronary acetylcholine (91). A recent study on the use of provocative testing at the initial presentation of MINOCA patients reported no complications (51). They demonstrated that provocative spasm testing in MINOCA cases suspicious for vasospasm was positive in about half of the patients (46.2%) with 64.9% having evidence of epicardial spasm and 35.1% microvascular spasm (51). Patients with coronary vasospasm (epicardial or microvascular) had a significantly higher risk of cardiac death than those without coronary spasm at a median 3-year follow-up (51).

CFR is assessed by the thermodilution or doppler flow velocity method in a hyperemic state using adenosine. CFR <2.0 is used to diagnose non-endothelial-dependent coronary microvascular dysfunction (77). Index of microvascular resistance (IMR) is another useful technique to assess coronary microvascular dysfunction by thermodilution with >25 used as the cut-off but is associated with lower sensitivity and specificity than CFR. Although coronary microvascular dysfunction is associated with an increased risk of MACE in INOCA patients (92), its prognostic impact on MINOCA patients is less clear. However, a recent meta-analysis demonstrated that a low CFR was predictive of mortality not only in patients with acute and chronic coronary syndromes but also in patients with heart failure, aortic stenosis, and systemic sclerosis (93).

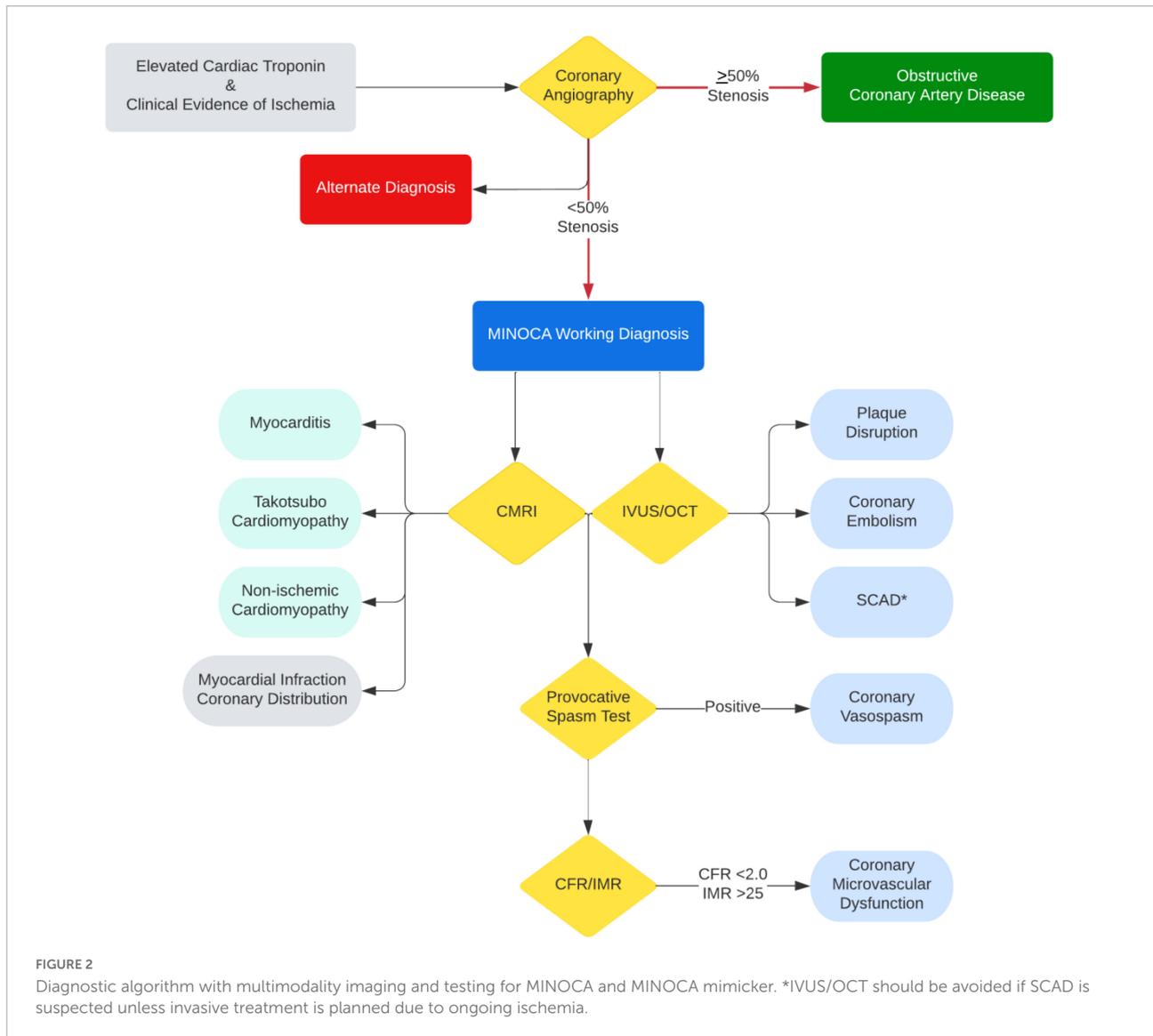
Multimodality approach

Multimodality imaging, both invasive and non-invasive, is critical to determining the underlying diagnosis of MINOCA. As outlined above, each modality has its limitations in reaching the underlying diagnosis; however, the diagnostic yield significantly improves when coupled (94, 95). The HARPP study demonstrated the combination of OCT and CMRI resulted in a diagnosis in 85% of the cases whereas OCT alone was diagnostic in 46% and CMRI alone in 74% of cases (27). Therefore, in a timely manner, CMRI needs to be performed for all patients with suspected MINOCA where a diagnosis remains uncertain. Further, IVUS or OCT of all three vessels is warranted at the time of angiography to identify intracoronary mechanisms leading to MINOCA. And in appropriate cases, provocative spasm testing with acetylcholine and measurement of CFR and/or IMR should be considered (Figure 2).

Treatment

The management strategies for MINOCA should be tailored to the underlying diagnosis (96). For example, aspirin and high-intensity statin should be used in patients with plaque disruption. In addition, those with plaque disruption not undergoing stenting may be treated with dual antiplatelet therapy by adding ticagrelor for \leq 1 month, based on the low revascularization rates at 1- and 4-year follow-up, 5.7 and 21.1%, respectively (97). Beta-blocker and renin-angiotensin system inhibitors should be considered in those with left ventricular dysfunction (4). Long-acting calcium channel antagonists (dihydropyridine and non-dihydropyridine) are used widely in MINOCA patients secondary to epicardial coronary vasospasm given that mechanistically they relax vascular smooth muscles secondary to suppressed Ca^{2+} flow (4). In cases of refractory variant angina, nitrates can be added to calcium channel antagonists, which enables vascular smooth muscle relaxation through nitric oxide reduction (98). Coronary embolism or thrombosis are treated with antithrombotic agents and targeted therapies for underlying thrombophilia (99).

Based on non-randomized observations, conservative management is favored in patients with SCAD over percutaneous coronary intervention (PCI), given that majority of dissections heal with conservative management and the increased risk of complications with intervention (30). PCI should be reserved for those with STEMI, cardiogenic shock, or ongoing ischemia. The use of antithrombotic agents in SCAD is controversial during the acute event (100). Secondary prevention medications in SCAD, such as aspirin, beta-blocker, statin, and renin-angiotensin system inhibitors, should be assessed based on the individual's risk factors (29). Data on treating coronary microvascular dysfunction is limited and



derived from patients with INOCA, where statins and renin-angiotensin system inhibitors have been shown to improve CFR (101). Antianginal treatment with B-blockers, calcium channel antagonists, and ranolazine for patients with chest pain is utilized (101).

Management of MINOCA mimickers is predominantly supportive care and guideline directed medical therapy for heart failure although data on this is limited. Majority of patients with Takotsubo cardiomyopathy have spontaneous recovery of normal cardiac function (63). However, those with left ventricular dysfunction are treated with beta-blockers and renin-angiotensin system inhibitors, and those with progressive circulatory failure may require mechanical circulatory support (102). Myocarditis often resolves in most patients within 2–4 weeks. However, in patients that develop arrhythmia and persistent cardiac dysfunction guideline-directed medical therapy (69). Physical activity should be avoided in the acute

phase and up to 6 months (69). There are ongoing trials assessing targeted treatment options for underlying etiologies, including anti-virals and immunosuppressives, that will provide better insight into targeted therapies in the future (68).

Secondary prevention medications are less frequently utilized in MINOCA patients than in those with obstructive CAD (103–106). A large multi-center, registry-based cohort study of patients with CAD undergoing cardiac catheterization ($n = 1,489,745$) reported that prescriptions of aspirin, statin, B-blocker, and renin-angiotensin system inhibitors were significantly lower in patients with non-obstructive coronary arteries than those with obstructive CAD ($p < 0.0001$ for each) (104). Not only at discharge but even at 1-year follow-up, secondary prevention medications were used substantially lower in patients with non-obstructive than those with obstructive CAD, as reported in a *post hoc* analysis of the multicenter prospective registry (105).

Studies have demonstrated significant benefits of secondary prevention in MINOCA patients. For example, in an extensive nationwide registry of patients with AMI in Sweden, MINOCA patients discharged on statins and renin-angiotensin system inhibitors experienced 23 and 18% lower risks of any MACE during a mean follow-up of over 4 years (14). Likewise, a Korean national registry reported that the lack of statins and renin-angiotensin system inhibitors at discharge in MINOCA patients increased the risk of 2-year all-cause of death by more than twofold in a multivariable-adjusted analysis (5). In addition, a meta-analysis of five observational studies reported 35% reduced mortality risk with statin treatment in MINOCA patients (HR: 0.65; 95% CI: 0.56–0.75) (107). Antiplatelet therapy is a cornerstone in managing obstructive coronary arteries; however, its role is less clear in MINOCA patients. For example, there was a trend toward increased risk of harm with aspirin in a small retrospective analysis (108), and with clopidogrel in a *post hoc* analysis (109).

Management of MINOCA is based on retrospective analyses with several limitations and potential biases. Therefore, it is essential to design randomized control trials to improve outcomes in MINOCA patients. In that respect, two randomized control trials are underway; NCT03686696 investigates the benefit of renin-angiotensin system inhibitors and B-blockers with a 2:2 factorial design in MINOCA patients and NCT04538924 compares two treatment groups (statin, renin-angiotensin system inhibitor, B-blocker, and dual-antiplatelet therapy vs. statin and renin-angiotensin system inhibitor) with a 1:1 ratio in MINOCA patients (110, 111). Further, a randomized PROMISE trial, NCT05122780, is underway, assessing precision medicine vs. standard of care for the underlying cause of MINOCA (112).

Conclusion

MINOCA is a syndrome that predominately affects females with a heterogenous working diagnosis that is understudied, underdiagnosed, and undertreated. MINOCA has similar prognosis compared to patients with MI and obstructive CAD. Therefore, diagnostic workup that includes multimodality advanced imaging, is essential to identify the underlying mechanisms and guide treatment. Randomized clinical trials on secondary prevention are underway but further research is needed to guide specific treatment of underlying mechanism.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for this study in accordance with the local legislation and institutional requirements. Written informed consent was not required for this study in accordance with the local legislation and institutional requirements.

Author contributions

MY, NA, AS, and MP reviewed the literature, wrote, and edited the manuscript. OQ and TH created outline for the manuscript, wrote, revised, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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