American Heart Association.

Myocardial Infarction With Nonobstructive Coronary Arteries: A Call for Individualized Treatment

Debabrata Mukherjee, MD, MS

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous clinical entity, characterized by clinical evidence of myocardial infarction (MI) with nonobstructive coronary arteries on angiography (≤50% stenosis) and without an overt cause for the MI, such as cardiac trauma or injury.[1] MINOCA is not uncommon and has been reported in 5% to 15% of individuals presenting with MI, depending on the population studied.[2,3] There are a variety of causes that can cause MINOCA, and it is important that patients are diagnosed with the correct underlying pathological condition so that specific therapies to treat the underlying cause can be prescribed. The most common causes of MINOCA appear to be coronary plaque disruption, coronary dissection, coronary artery spasm, microvascular disease, coronary thromboembolism, and, finally, MINOCA of uncertain cause.[3] Coronary plaque disruption, which includes plaque rupture, plaque erosion, and calcific nodules, is common among patients with MINOCA and can trigger thrombus formation that leads to MI via distal embolization, superimposed vasospasm, and transient complete thrombosis with spontaneous thrombolysis. Coronary artery vasospasm, another potential cause of MINOCA, defined as marked (ie, >90%) constriction of an epicardial coronary artery with diminished myocardial blood flow, may occur either in response to drugs or toxins or spontaneously caused by abnormal coronary vasomotor tone. Although coronary microvascular dysfunction typically presents as stable ischemic heart disease,[4] it is also considered a potential cause of MINOCA.[2] Microvascular dysfunction can be a cause of ischemia but can also be an effect of myocardial injury of either ischemic or nonischemic origin.[5] The precise contribution of coronary microvascular dysfunction in MINOCA requires additional study, assessing the roles of microvascular angina, microvascular spasm, or the coronary slow flow phenomenon in patients with MINOCA. Coronary embolism may cause MINOCA if it lodges in the microcirculation or if lysed partially in the epicardial coronary artery with resultant nonobstructive or <50% angiographic disease. Finally, some patients with spontaneous coronary artery dissection may appear to have nonobstructive coronary artery disease on angiography because of gradual tapering of the vessel; and this can, therefore, be a potential cause of MINOCA. The diagnosis of a type 2 MI or supply demand mismatch is made in patients with MINOCA when a potential cause exists, such as tachycardia, severe anemia, or hypotension, without evidence of any other pathological condition that would identify another cause.[6]

Although the treatment of MI with obstructive coronary artery disease is well established, there is a paucity of randomized data on the effectiveness of preventative therapies for individuals with MINOCA. In this issue of the *Journal of the American Heart Association* (*JAHA*), Choo et al[7] analyzed factors related to all-cause death in MINOCA using a nationwide, multicenter, and prospective registry. They report that patients with MINOCA and those with MI related to obstructive coronary artery disease had comparable clinical outcomes. They also report that the use of renin-angiotensin system blockers and statins was associated with lower mortality in patients with MINOCA. These results appear concordant with the stratified propensity analysis of 9138 patients with MINOCA enrolled in the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy) registry, which reported that after a mean follow-up of 4.1 years, there was a significantly lower rate of all-cause mortality, hospitalization for MI, ischemic stroke, and heart failure associated with the use of statins (hazard ratio, 0.77

[95% CI, 0.68–0.87]) and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) (hazard ratio, 0.82 [95% CI, 0.73–0.93]) and a trend for a lower event rate with the use of β-blockers (hazard ratio, 0.86 [95% CI, 0.74–1.01]).[8] However, the use of dual-antiplatelet agents was not associated with a lower event rate (hazard ratio, 0.90 [95% CI, 0.74–1.08]). The ongoing MINOCA BAT (Randomized Evaluation of β-Blocker and ACEI/ARB Treatment in MINOCA Patients; ClinicalTrials.gov Identifier: NCT03686696) study will randomize ≈3500 patients with MINOCA to treatment with ACEIs/ARBs and β-blockers or matching placebo. The primary end point of the study is time to death of any cause or readmission because of MI, ischemic stroke, or heart failure and should provide us with valuable information on the benefits or risks of routine cardioprotective therapies in patients with MINOCA. One modest-sized randomized study, the BHF CorMicA (British Heart Foundation Coronary Microvascular Angina) study, tested stratified medical therapy for patients with MINOCA, guided by an interventional diagnostic procedure,[9] and reported that this strategy of vasoreactivity testing to guide treatment is feasible and improves angina in patients with nonobstructive coronary artery disease. This study had

several limitations, including using binary cutoffs for the vasoreactivity study, potential bias in symptom ascertainment because the patient and cardiologist were not blinded to group allocation, and potential selection bias in patient enrollment because a considerable proportion of patients undergoing invasive coronary angiography were not enrolled, primarily because of patient preference. Given these limitations, additional studies are indicated to validate these results and the role of vasoreactivity testing among those presenting with MINOCA.

While we await the results of MINOCA BAT and other randomized studies, on the basis of available data and the scientific statement from the American Heart Association on MINOCA,[2] we suggest an individualized approach to the management of patients with MINOCA on the basis of the underlying cause (Figure). The central principle in the management of MINOCA is to elucidate or identify the underlying mechanism for targeted therapies and optimize outcomes. In general, ACEI or ARB and statins should be considered for most patients with MINOCA.

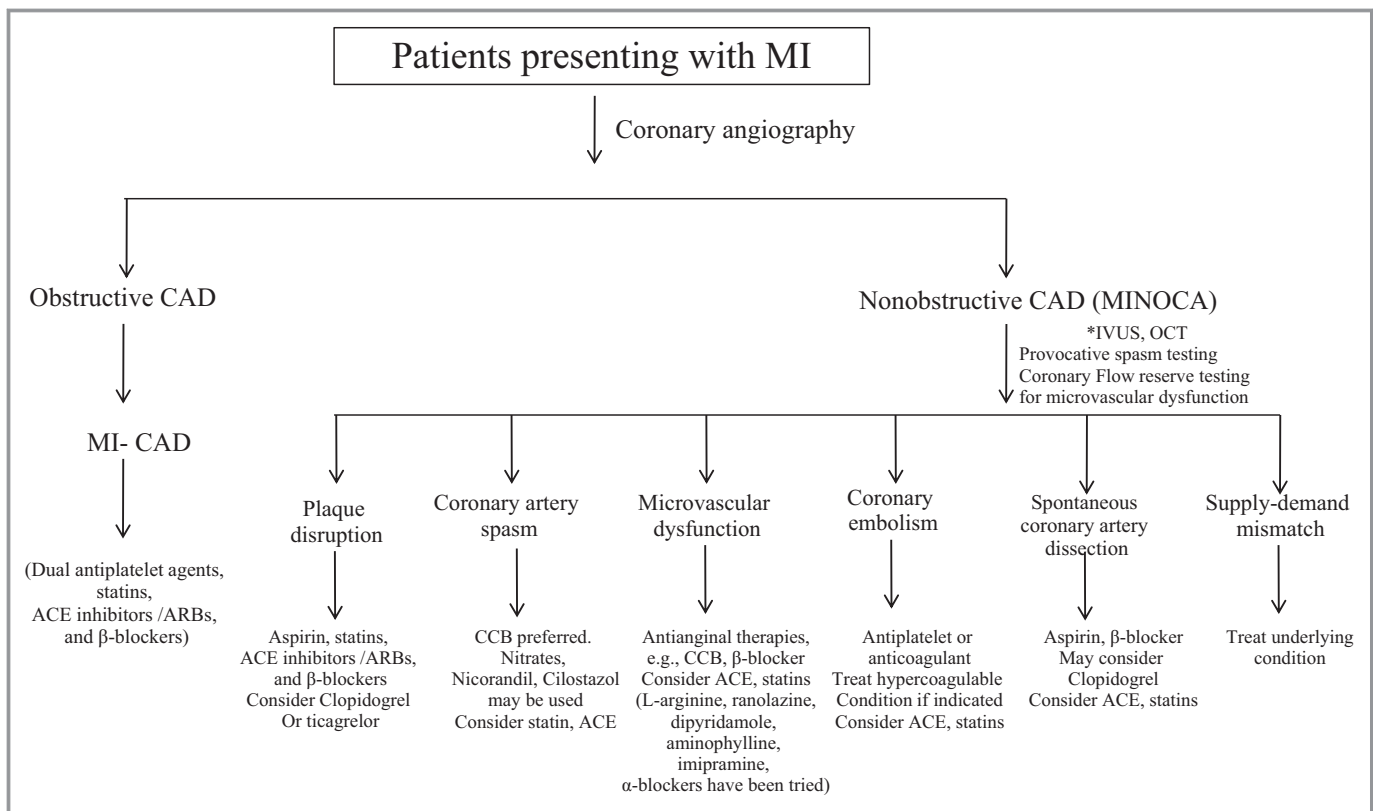The prognosis of patients with MINOCA depends on the underlying cause, but overall it is not a benign condition, as

Figure. Individualized approach to the management of patients with myocardial infarction (MI) with nonobstructive coronary arteries on the basis of the underlying cause. *Additional investigations that may be considered in addition to routine evaluation for patients with acute MI and nonobstructive (<50%) coronary artery stenosis. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; IVUS, intravascular ultrasound; MINOCA, MI in the absence of obstructive coronary artery disease; OCT, optical coherence tomography.

reported in the current study by Choo et al[7] and other studies, such as the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI [Acute MI] Patients) study, with patients with MINOCA having similar mortality rates and comparable quality-of-life measures as patients with obstructive coronary artery disease.[10] Additional studies are indicated to assess the optimal therapies for patients presenting with MINOCA, focusing on hard clinical end points, such as mortality and reinfarction. In addition to the hard cardiovascular end points, the impact of MINOCA on quality of health also needs to be evaluated on parameters such as persistent angina, activities of daily living, and depression.[11] For now, on the basis of limited data, it seems reasonable to administer ACEIs/ARBs, statins, and antiplatelet agents to most patients presenting with MINOCA while we await more robust prospective randomized data.

Disclosures

None.

References

1. Pasupathy S, Tavella R, McRae S, Beltrame JF. Myocardial infarction with non-obstructive coronary arteries: diagnosis and management. *Eur Cardiol*. 2015;10:79–82.

2. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, Bolger AF, Beltrame JF; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Quality of Care and Outcomes Research. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e891–e908.

3. Scalone G, Niccoli G, Crea F. Editor's choice: pathophysiology, diagnosis and management of MINOCA: an update. *Eur Heart J Acute Cardiovasc Care*. 2019;8:54–62.

4. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation*. 2017;135:1075–1092.

5. Mauricio R, Srichai MB, Axel L, Hochman JS, Reynolds HR. Stress cardiac MRI in women with myocardial infarction and nonobstructive coronary artery disease. *Clin Cardiol*. 2016;39:596–602.

6. Neumann JT, Sorensen NA, Rubsamen N, Ojeda F, Renne T, Qaderi V, Teltrop E, Kramer S, Quantius L, Zeller T, Karakas M, Blankenberg S, Westermann D. Discrimination of patients with type 2 myocardial infarction. *Eur Heart J*. 2017;38:3514–3520.

7. Choo EH, Chang K, Lee KY, Lee D, Kim JG, Ahn Y, Kim YJ, Chae SC, Cho MC, Kim CJ, Kim H-S, Jeong MH; KAMIR-NIH Investigators. Prognosis and predictors of mortality in patients suffering myocardial infarction with non-obstructive coronary arteries. *J Am Heart Assoc*. 2019;8:e011990. DOI: 10.1161/JAHA.119.011990.

8. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation*. 2017;135:1481–1489.

9. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K, Hood S, McGeoch R, McDade R, Yii E, Sidik N, McCartney P, Corcoran D, Collison D, Rush C, McConnachie A, Touyz RM, Oldroyd KG, Berry C. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol*. 2018;72:2841–2855.

10. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, Reynolds HR, Geda M, Bueno H, Dziura JD, Krumholz HM, D'Onofrio G. Presentation, clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO study. *J Am Heart Assoc*. 2018;7:e009174. DOI: 10.1161/JAHA.118.009174.

11. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153.