

## Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): It's Time to Face Reality!

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Although the occurrence of an acute myocardial infarction (AMI) without significant coronary artery disease (CAD) was initially reported almost 80 years ago,<sup>1</sup> the term *MINOCA* (myocardial infarction with nonobstructive coronary arteries) has been used only recently to describe these patients.<sup>2</sup> A sizeable minority of patients with AMI are found to have MINOCA.<sup>3–11</sup> Unfortunately, some physicians fail to realize that the absence of obstructive coronary arteries does not exclude the possibility of an AMI. As such, patients with MINOCA may be misinformed about their diagnosis and inaccurately “reassured” about a favorable prognosis. Even when appropriately diagnosed, the management of this heterogeneous group of patients will vary depending on local practices and hospital resources. Over the past several years, a blossoming body of literature on MINOCA has examined this unique syndrome to guide clinicians caring for such patients.

It is in this context that the work by Safdar and colleagues<sup>12</sup> in this issue of the *Journal of the American Heart Association (JAHA)* should be viewed. The authors reported on the incidence, etiologies, and outcomes of patients with MINOCA included in the VIRGO (Results From the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study. They demonstrated that in young patients (aged <55 years) presenting with AMI, MINOCA is relatively frequent, occurring in >10% of the population. Although the characteristics of patients with MINOCA and their counterparts with AMI and CAD (AMI-CAD) were different, the mortality rates at 1 month (1.1% versus 0.6%,  $P=0.43$ ) and 1 year (1.7% versus 2.3%,  $P=0.68$ ) were not statistically different. Quality of life measures

were also comparable between the 2 groups. This multicenter study, in which sex-specific data were collected prospectively, outlines some key concepts related to MINOCA. First, MINOCA is not an uncommon presentation of AMI. It is more frequent in younger women and nonwhites, is associated with fewer traditional risk factors, and usually presents with non-ST-segment elevation–myocardial infarction. Second, patients with a working diagnosis of MINOCA should undergo further testing to uncover its underlying etiology. Third, MINOCA is not a benign syndrome, with younger MINOCA patients having outcomes comparable to their AMI-CAD counterparts.

MINOCA is found in roughly 6% of AMI patients<sup>4</sup>; however, there is large variability in its reported prevalence, with a range of 3.5% to 15%,<sup>3–11</sup> possibly attributable to differences in the studied populations and heterogeneity in its definition. MINOCA is also more common in younger patients and women.<sup>3–7</sup> This explains to a large extent why the current study, examining adult AMI patients aged <55 years, with a 2:1 enrollment ratio of women to men, reported a higher prevalence of MINOCA than earlier reports. In this study, women with AMI had 5-fold higher odds of having MINOCA than men with AMI, and 1 in 8 women with AMI were found to have MINOCA. It is also noteworthy that in the VIRGO study, all patients with spontaneous coronary artery dissection were categorized as MINOCA. However, some patients with spontaneous coronary artery dissection have obstructive disease, and this may have resulted in a larger-than-expected number of reported cases of MINOCA in the current study.

Some earlier reports outlining the occurrence of nonobstructive coronary arteries used less stringent inclusion criteria to define MINOCA, resulting in overestimation of its prevalence. In a systematic review of MINOCA studies,<sup>4</sup> for example, one-third of the included MINOCA patients who were referred for cardiac magnetic resonance imaging were found to have myocarditis instead of AMI, and close to 20% had magnetic resonance imaging findings suggestive of Takotsubo cardiomyopathy. Because the aforementioned conditions result in troponin elevation in the absence of myocardial ischemia, these patients should not be given a diagnosis of MINOCA. Troponin elevation is not always secondary to myocyte necrosis (eg, apoptosis, normal cell turnover) and can occur in the setting of other systemic conditions (eg, sepsis, heart failure, myocarditis, pulmonary embolism).<sup>13</sup> In keeping with the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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*J Am Heart Assoc.* 2018;7:e009635. DOI: 10.1161/JAHA.118.009635.

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definition of MINOCA outlined in the 2016 European Society of Cardiology position paper,<sup>14</sup> the term *MINOCA* should be reserved for those patients with an AMI (as defined by the “Third Universal Definition of Myocardial Infarction”<sup>15</sup>) in the absence of obstructive coronary arteries and no other clinical findings to suggest alternative causes for the elevated cardiac biomarkers. This highlights the importance of revisiting the initial diagnosis of AMI once nonobstructive coronary arteries are established angiographically and considering alternative diagnoses. This may help uncover other unrecognized conditions that lead to troponin elevation unrelated to myocardial ischemia and that often require different therapies (eg, immunosuppressive therapies for myocarditis, anticoagulant therapies for pulmonary embolism). Notably, in the current study, the investigators included only patients who were felt to have had a true AMI (requiring symptoms of myocardial ischemia and/or ECG changes in the setting of a rise and fall in cardiac biomarkers >99th percentile). Although they utilized either troponin or the less specific creatine kinase–MB biomarker, all patients underwent invasive coronary angiography, adding robustness to their findings. Patients with elevated cardiac markers due to presumed myocarditis or Takotsubo were not included in the VIRGO registry. This selective approach to defining these patients in the prospective multicenter VIRGO study helped provide a more accurate estimate of the true prevalence of MINOCA in an otherwise young AMI population. When examining MINOCA in future studies, it is important to use a strict approach to selection and a uniform and acceptable definition to maintain consistency and research rigor.

MINOCA is a syndrome resulting from myriad conditions. Additional testing to identify its underlying etiology is crucial so that etiology-targeted therapies can be implemented. A focused clinical history with a detailed assessment of the presenting symptoms, along with a family and social history, may provide diagnostic clues. When needed and if resources permit, additional testing should be considered, including intracoronary imaging studies with intravascular ultrasound or optical coherence tomography, thrombophilia testing, provocative testing for coronary vasospasm, and cardiac magnetic resonance imaging. Studies of intracoronary imaging have shown that  $\approx 40\%$  of patients with MINOCA have some evidence of plaque disruption.<sup>16,17</sup> Although intravascular ultrasound is helpful in demonstrating plaque rupture,<sup>16</sup> optical coherence tomography is a better tool for identifying patients with plaque erosion<sup>18</sup> and may be superior for the assessment of patients with spontaneous coronary artery dissection.<sup>19</sup> In the current report, intracoronary imaging was not routinely utilized, and that may explain why a large number of patients with MINOCA were “undefined.” Thrombophilia disorders can be detected in up to 14% of MINOCA patients<sup>4</sup>; however, a hypercoagulability syndrome was detected in only 3% of MINOCA patients in the current

report, casting doubt on whether extensive thrombophilia testing was really undertaken in VIRGO. Provocative spasm has been detected in  $\approx 27\%$  of MINOCA patients,<sup>4</sup> with even higher rates noted in Asian populations.<sup>4,20</sup> In VIRGO, however, only a few patients underwent formal provocative testing for coronary vasospasm. The extent of required testing in patients with a presumptive diagnosis of MINOCA depends on the patient’s clinical presentation. In a young female smoker, for example, with a family history of factor V Leiden deficiency,<sup>21</sup> a hypercoagulable state is the most likely diagnosis, and one should focus on thrombophilia testing as the first diagnostic step. Although additional testing should always be considered, it may not be feasible because of costs, availability, and other considerations. At times, even extensive assessments may be inconclusive. In these cases, patients may fall into a category of unclassified MINOCA.

Given the absence of significant atherosclerosis, it is intuitive that the prognosis of patients with MINOCA is better than that for myocardial infarction and CAD (MI-CAD). In fact, many studies have suggested a more favorable prognosis for patients with MINOCA compared with patients with MI-CAD.<sup>3–5,7,11</sup> In contrast, a few studies have shown similar or worse outcomes for MINOCA patients.<sup>9,22</sup> Pooled data of MINOCA studies reported 0.9% and 4.7% in-hospital and 1-year mortality rates, respectively.<sup>4</sup> In the large Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy (SWEDEHEART) registry,<sup>23</sup> 24% of MINOCA patients experienced a major cardiovascular event (a composite of all-cause death, rehospitalization for AMI, ischemic stroke, or heart failure) during a mean follow-up of 4.5 years, including a 14% mortality rate. In the current study, mortality rates for MINOCA patients were numerically lower but not statistically different than their AMI-CAD counterparts. Whether the comparable mortality between both AMI syndromes is real or a spurious finding related to the lower mortality event rates in the current study (ie, underpowered analysis) remains to be seen. Of note, mortality rates for MINOCA patients enrolled in the VIRGO registry were twice as high as those reported in a healthy population of young female patients.<sup>24</sup> Furthermore, a similar proportion of patients with MINOCA and MI-CAD presented in cardiac arrest or heart failure. Functional and psychosocial outcomes were also comparable between MINOCA and MI-CAD patients. VIRGO adds tremendously to the MINOCA body of literature by providing detailed health status and psychosocial comparative data. Although it is possible that outcomes may vary according to the underlying etiology for MINOCA, the VIRGO registry had too few patients with etiology-specific diagnoses to draw any firm conclusions. Overall, on the basis of many contemporary studies, it is clear that MINOCA is not a benign condition, and patients should be appropriately counseled and treated.

It is interesting to note that among patients with AMI, there is a higher prevalence of nonobstructive coronary arteries among women, particularly young women.<sup>25–30</sup> Nevertheless, the prognosis for young women with AMI is worse than that for young men.<sup>26,29,31–34</sup> It is possible that this result is due to suboptimal (less aggressive and/or less targeted) therapeutic strategies in patients with “nonatherosclerotic” AMI. This is in keeping with the current study, in which 90% of MINOCA patients were women, and discharge therapies (eg, aspirin,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers, and statins) were less frequently prescribed for MINOCA patients. Observational data from the SWEDEHEART registry reported favorable outcomes when MINOCA patients were treated with  $\beta$ -blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers, and statins, but no significant benefits were observed with P2Y<sub>12</sub> inhibitors.<sup>35</sup> Although the aforementioned data suggest a benefit from routine cardio-protective therapies,<sup>35</sup> no randomized controlled trial data are available to inform clinicians on best practices. The MINOCA BAT (Randomized Evaluation of  $\beta$ -Blocker and Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Treatment in MINOCA Patients) study is expected to begin enrollment in Europe in 2018 (with plans to expand enrollment to the United States and Canada in the next year). This study aims to randomize >5600 MINOCA patients to treatment with oral angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers and  $\beta$ -blockers versus matching placebo and will examine rates of death and other cardiovascular events at 1 year. Until then, the indications for  $\beta$ -blockers and angiotensin-converting enzyme inhibitors and angiotensin receptor II blockers are less robust in MINOCA patients but maybe considered on the basis of the SWEDEHEART registry data.<sup>23</sup> While awaiting the results of this important trial, it is reasonable to consider therapies including aspirin and statins for any patient with established atherosclerotic cardiovascular disease.

In summary, MINOCA occurs frequently in young women with AMI and has comparable outcomes to MI-CAD up to 1 year of follow-up. Nevertheless, there is a paucity of evidence-based data to guide our approach to the evaluation and management of MINOCA patients. This results in variable and suboptimal practice patterns and disparities in care. The time has come to make a change! To favorably affect outcomes, we must erase all prior misperceptions regarding this condition and institute appropriate long-term investigations examining a wide array of diagnostic and therapeutic strategies in MINOCA patients.

## Disclosures

None.

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**Key Words:** Editorials • coronary artery disease • myocardial infarction • prognosis • sex