

Title: Type 2 MI and the Sex Divide: Moving from Awareness to Action

Authors: Melody Huang, MD^a and Nicholas Phreaner, MD^a

Affiliation: ^aDivision of Cardiovascular Medicine, Department of Medicine, University of California San Diego, La Jolla, California, USA.

Corresponding Author:

Nicholas Phreaner, MD

Sulpizio Cardiovascular Center, University of California San Diego

9452 Medical Center Drive #7411, La Jolla, CA 92037, USA

E-mail: nphreaner@health.ucsd.edu

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Type 2 myocardial infarction (T2MI) confers a poor prognosis, including a two-fold rate of all-cause mortality at five years when compared to type 1 MI and at least similar rates of other MACE events [1]. Sex differences in the management and outcomes of patients with type 1 MI are well-established - men are more likely to have a type 1 event; women with a type 1 MI are less likely to receive revascularization and guideline-directed medical therapy and have a higher excess mortality rate. However, sex differences related to T2MI are less well understood but may warrant even greater attention, as T2MI disproportionately affects women. Moreover, sex-

specific pathophysiological processes, such as spontaneous coronary artery dissection (SCAD) and microvascular dysfunction, are more prevalent in women and may further accentuate these differences.

Over recent years, only a few studies have aimed to address this question. A single-center study of 359 patients [2] and a larger study using the SWEDEHEART registry of 5442 patients [3] both found that women with T2MI were older and had less prevalent coronary artery disease (CAD) than men. Rates of coronary angiography were also similar between men and women, but men were more likely to have obstructive CAD and a low ejection fraction. While mortality and readmission rates at ninety days were similar in the single-center study, results from the SWEDEHEART registry suggested that men with T2MI had a higher risk of all-cause mortality and MACE when compared with women, even after adjusting for cardiac comorbidities. Separately, a smaller study of 50 patients with T2MI and coronary CT angiography results showed that men and women had similar rates of prevalent CAD as well as coronary plaque burden and hemodynamically significant CAD by FFR analysis [4]. However, women had lower amounts of low-attenuation plaque.

The variability in these findings and the limited available evidence may reflect the inherent challenges in diagnosing, and thus studying, T2MI. Diagnosing the exact pathology responsible for a T2MI remains difficult, particularly in cases lacking a clear etiology for increased myocardial oxygen demand. There are no strong evidence-based guidelines to support clinicians in distinguishing between different mechanisms of reduced myocardial oxygen supply as the underlying cause of T2MI, whether it is vasospasm, coronary embolus, or microvascular disease,

to name a few. Thus, in most instances, treatment of a T2MI is condensed to treatment of underlying cardiovascular risk factors, and evidence-based management of the specific pathophysiologic mechanism is lacking. This topic is thus worthy of a high-quality review paper to discuss, and raise awareness, of this challenging diagnosis.

In this issue of *Trends in Cardiovascular Medicine*, Angeli *et al.*, on behalf of the Italian Society of Cardiology Working Group on Gender Cardiovascular Diseases, provide a comprehensive review of sex- and gender-based differences in T2MI [5]. The authors outline the pathophysiology of T2MI and examine how sex and gender influence its incidence, clinical presentation, and underlying etiologies. In addition to reviewing the current literature, they explore underlying sex-based anatomic and physiologic differences, as well as gender-related social and cultural factors, in order to provide context and potential mechanistic explanations for the observed disparities in observational studies. This perspective adds valuable depth to the current understanding of T2MI and lays the groundwork for proposed future directions in sex- and gender-specific diagnostic and therapeutic strategies.

Importantly, the review elucidates sex-specific biological mechanisms contributing to the differential prevalence of T2MI etiologies between men and women. For example, estrogen has cardioprotective effects through its anti-inflammatory properties and maintenance of vascular tone via vasodilation. This may partly explain the increased incidence of microvascular dysfunction and vasospasm observed in postmenopausal women. Hormonal differences may also underlie the increased rates of epicardial vasospasm in males and microvascular dysfunction in females.

The authors should be commended for producing a timely and well-researched manuscript that effectively summarizes the current state of knowledge. They also propose promising future directions, including the development of sex-specific biomarkers, advanced imaging approaches and the application of artificial intelligence to better characterize sex- and gender-based differences and guide individualized treatment strategies.

While we agree that artificial intelligence represents an exciting new tool with the potential to enhance diagnostic accuracy within this challenging diagnosis and uncover novel therapeutic targets, we emphasize the continued importance of more traditional research approaches. In particular, there remains a critical need for well-designed randomized clinical trials focused on evaluating treatments for the distinct conditions that lead to T2MI. Although SCAD, vasospasm and stress-induced (Takotsubo) cardiomyopathy, a mimicker of T2MI, may present at a lower incidence than atherosclerotic plaque rupture related type 1 myocardial infarct, these are not rare diseases by any means. These are regularly encountered clinically and should lend themselves to multi-center therapeutic trials. Although observational studies have brought welcome attention to this diagnosis, multi-center therapeutic trials are urgently needed. This could start with studying commonly used medications, such as beta blockers, statins and anti-platelet therapy for initial treatment and secondary prevention.

We believe that making progress in this disease may require a sex-specific approach to diagnosis and treatment, as sex-specific mechanisms underlie the pathophysiology of T2MI. Furthermore, the broad categorization of T2MI as supply-demand mismatch likely impedes in-depth investigation of and advancement in these disease processes, as each disease that causes T2MI

may be characterized by distinct risk factors, therapeutic responses, and prognoses. Ultimately, an optimal strategy for managing T2MI may involve a sex-specific approach tailored to each distinct subtype, rather than relying on a broad, one-size-fits-all method for this heterogeneous condition. Both cardiovascular patients and clinicians urgently require evidence-based guidance to inform clinical decision-making in this complex area.

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