

## Bridging the Sex Gap in Early Myocardial Infarction Mortality

### Why It Matters

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Cardiovascular disease (CVD) mortality in women surpassed that of men in 1984<sup>1</sup> triggering an intense focus to increase awareness, explore sex-specific influences, and enhance evidence-based treatment of CVD in women. These efforts have yielded benefit with declines in CVD mortality in women and subsequent elimination of the sex gap.<sup>1</sup> Despite these successes, overall declines in CVD mortality have leveled, and in 2012, heart disease deaths increased slightly.<sup>2</sup> Of particular concern are women aged 45 to 65 years who have increased rates of myocardial infarction (MI) associated with a higher in-hospital mortality than their male counterparts.<sup>3</sup>

#### See Article by Smilowitz et al

Sex differences are evident in pathophysiology, treatment, and outcomes of MI. Women are more likely to die in the first year after an MI, experience non-ST-segment-elevation MI, MI with nonobstructive coronary artery disease (MINOCA) and plaque erosion, and have lower rates of plaque rupture (76% versus 55%) compared with men.<sup>4,5</sup> Women are less frequently referred for appropriate treatment, have lower utilization rates for efficacious therapies, and experience higher rates of post-MI complications as compared with men.<sup>4</sup> These sex differences in pathogenesis and management of MI remain prescient topics for a 21st-century cardiovascular research agenda.

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Smilowitz et al<sup>6</sup> report an analysis of age, sex, and outcome differences in MINOCA and MI with obstructive coronary artery disease (MI-CAD) in a contemporary data set—the NCDR (National Cardiovascular Data Registry) ACTION Registry-GWTG (Acute Coronary Treatment Intervention Outcomes Network Registry—Get With the Guidelines). Consistent with previous reports, the authors found that MINOCA was rare among patients with MI and was associated with lower mortality in comparison with MI-CAD. However, the discovery that higher post-MI mortality in women as compared with men was driven by the MI-CAD group and pronounced at

younger ages is an important new contribution to the literature. The findings raise several key questions that may provide future directions for further research: (1) How do we explain this paradox of increased mortality among young women with MI-CAD at a time of presumed protection from CVD? (2) What exactly is the heterogeneous condition of MINOCA, why is it more common in women, and how can we refine our phenotyping to better define risk and therapeutic options? (3) What are the predictors and long-term outcomes of increased post-MI mortality in women, and how generalizable are the findings?

#### Mortality Paradox in Young Women

The article's most intriguing finding revealed that the higher risk of post-MI death among women compared with men was restricted to the MI-CAD group and particularly young women. This is a notable contribution to the understanding of MI and associated sex differences in post-MI mortality.

Increasing evidence indicates that young women with obstructive MI are fundamentally distinct. The challenge and opportunity is to extend analyses, such as the one by Smilowitz et al, to examine explanatory hypotheses that will advance our understanding of the predictors and prospects for prevention and intervention in this age–sex group. Prior reports indicate delays in presentation, lack of early detection, and lower use of guideline-directed medical therapy among women with MI. How do these factors specifically relate to young women with MI-CAD and their higher mortality than age-matched male counterparts or older women? Further, how do these clinical factors interact with exposures, differential risk factors, and their potency, genetic susceptibility, and lifestyle and social determinants of health to affect outcomes in young women with MI-CAD? Understanding the complex interplay of risk that can essentially negate the protective effects of young age in this age–sex group is essential to our understanding of tailored prediction, prevention, and treatment. Perhaps, young women with MI-CAD represent an inherently high-risk phenotype or genetic susceptibility that would provide insights for early MI phenotypes across sex and race groups. With the tools in our repertoire today to identify new signals and determinants of risk, subphenotypes, and therapeutic responses, research stands poised to unravel this paradox and further our understanding of the primary drivers of MI in young women that could transform our approaches to prediction and prevention.

#### What Exactly Is MINOCA, and Why Is It More Common in Women?

In the analysis by Smilowitz et al,<sup>6</sup> MINOCA was more common among women as compared with men, occurred in ≈6%

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of patients with MI, and was associated with younger age and lower in-hospital and 12-month mortality than individuals with MI-CAD.

MINOCA seems to be a unique clinical entity with specific risk, mechanisms, and outcomes. The heterogeneity of MINOCA and its underlying pathogenesis present challenges to the understanding and treatment of MI. Imaging studies and biopsies report underlying diagnoses of subendocardial infarct, myocarditis, Takotsubo cardiomyopathy, and hypertrophic cardiomyopathy, to name a few.<sup>5</sup> Coronary artery vasospasm is reported to be inducible in about a quarter of patients with MINOCA in some studies. Inherited thrombotic disorders have also been associated with MINOCA presumably leading to coronary thrombosis or embolism as causes of MI.<sup>5</sup> Prior reports, such as the National Heart, Lung, and Blood Institute–sponsored WISE study (Women’s Ischemia Syndrome Evaluation), identified the higher likelihood of coronary microvascular disease as one specific pathophysiology of MINOCA in women.<sup>7</sup>

A limitation of the analysis using the ACTION Registry-GWTG is the inability to discern mechanisms of disease that data, such as intravascular imaging or cardiac magnetic resonance imaging, could provide. Understanding pathogenesis and its distribution across age groups may provide insights into why this condition tends to occur in women and at younger ages. Integrated research that allows analyses across registry, clinical, imaging, and exposure data can advance understanding of risk profiles and optimal treatment strategies, elucidating why conditions such as MINOCA are more prevalent in women, and expounding on drivers of MINOCA’s associated 5% 1-year mortality and 5% rate of in-hospital major adverse cardiovascular events.<sup>5</sup> Tailored therapy based on pathogenesis may be the more responsive approach to improving long-term survival and reducing recurring cardiac events for patients with MINOCA.

Smilowitz et al also found a higher likelihood of MINOCA among black patients of both sexes compared with their counterparts. Black women have a higher prevalence of MI than other women, including higher rates of sudden cardiac death.<sup>4</sup> Findings from the National Heart, Lung, and Blood Institute Multi-Ethnic Study of Atherosclerosis reveal that blacks and women have less plaque burden and coronary artery calcium than their white and male counterparts, respectively. This generates hypotheses of differing pathophysiology of disease with plaque erosion—as opposed to rupture—being a more prominent feature of MI in blacks compared with whites.<sup>1</sup> Understanding the intersection of race, sex, and MI phenotypes on outcomes remains a critical area of scientific inquiry where a systems approach of integrated data analysis presents unique opportunities.

Given its complexity and heterogeneity, further elucidating mechanisms of MINOCA may represent an essential next step in refining prediction and tailoring therapies for patients.

### Long-Term Outcomes and Generalizability

In the report by Smilowitz et al, ≈50% of subjects were excluded from the analysis, including those with cardiac arrest, prior cocaine use, lack of angiographic data, and missing variables, such as sex. Although reasonable rationales distinguish

these individuals from the cohort of analysis, their exclusion does potentially introduce selection bias into the analysis. For example, among those without angiographic, age, or sex data, it is unclear whether the proportions of MINOCA and MI-CAD were similar to the data set used for analysis and whether the age and sex-related findings of mortality and outcomes were also similar, limiting the broader generalizability of the findings.

The ACTION Registry-GWTG data set is inherently limited in its ability to examine longer-term outcomes because data collection does not extend beyond hospitalization. A comparison of longer-term mortality and recurrent events could provide insight on implications of the findings of the analysis. For example, the effects of sex-based differences in treatment and management of women with MINOCA or MI-CAD are unclear, and it is unknown whether sex differences in-hospital mortality for this cohort persist, attenuate, or worsen over time.

### Conclusions

The report by Smilowitz et al examining MI mortality by sex, age, and coronary artery disease status provides a unique contribution to the literature as one of the few studies that has elucidated an MI phenotype driving higher post-MI mortality among women. This report demonstrates the importance of examining sex as a biological variable throughout every phase of research from hypothesis generation, through research design, and ultimately analysis. Such research begins to close gaps in our understanding of sex differences in coronary pathophysiology, illuminates needs for tailored diagnostic testing and optimal pharmacological and interventional strategies, and enhances recognition that the cardiovascular health of all Americans requires a continued multipronged and multidisciplinary research approach.

The National Heart, Lung, and Blood Institute Strategic Vision<sup>8</sup> identifies research priorities relevant to women’s cardiovascular health across all 8 of its objectives. Relevant to MI in women is the importance of understanding normal biology including examining resilience and hormonal influences on cardiac function; pathobiology and sex differences in mechanisms of diseases, such as those that may contribute to the paradox of higher mortality of MI-CAD in younger women; and population differences and specific contributions to diseases that present only in women, are more prevalent in women, or have prominent sex differences, such as MINOCA. The vision promotes the promise of precision medicine, and when fully realized, embraces sex as the highest order of tailored risk assessment, prevention, diagnosis, and treatment of MI, leveraging integrated approaches of data science to enhance analysis of exposure, genomic, phenome, clinical, and imaging data. It envisions a future where novel diagnostics encompass the contribution of unique sex-based biomarkers of disease and clinical and implementation research that advances sex-specific analyses to eliminate gaps in evidence-based care of MI in women.

Moving toward an understanding of sex as the highest order of our futuristic approach to precision medicine recognizes the opportune timing for deeper phenotyping that will more accurately define subphenotypes of disease, more

clearly identify those at risk, personalize prevention, and develop tailored therapeutic strategies to address underlying pathophysiology.

### Disclosures

None.

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