

# Even When the Heart Stops, the Sex Differences Remain



Cardiovascular disease remains the leading cause of death in women,<sup>1</sup> but mechanisms of sex-related differences that affect many facets of cardiovascular disease remain underrecognized and poorly understood. Men historically have been disproportionately represented in clinical studies, and consequently, guidelines have been built on data that are predominantly applicable to men.<sup>1</sup> There has recently been an increasing commitment to better understand sex-related differences that affect the epidemiology, presentation, diagnosis, treatment, and outcomes of cardiovascular disease.<sup>1</sup>

Mortality rates after out-of-hospital cardiac arrest (OHCA) remain high, with 9% of those with emergency medical services—treated OHCA surviving to hospital discharge in the United States.<sup>2</sup> Prior studies have consistently reported that women experiencing OHCA are older, more likely to have an unwitnessed OHCA, and less likely to have a shockable rhythm at presentation.<sup>1-4</sup> Several studies have also reported lower rates of bystander cardiopulmonary resuscitation for women,<sup>1,3,4</sup> largely because of hesitancy to expose a woman's chest in public. Interestingly, despite these unfavorable associations for women with OHCA, studies evaluating sex-related differences in survival after OHCA have reported conflicting results.<sup>3,4</sup> In addition, it remains unclear what the relative contributions of biologic mechanisms and differences in health care delivery are to mortality, both immediately and after OHCA.

In this issue, Dafaalla et al<sup>5</sup> further explore sex-related differences in OHCA outcomes in the setting of acute myocardial infarction (AMI). Data were collected from the Myocardial Ischaemia National Audit Project (MINAP), resulting in a large retrospective cohort of 16,278 adult patients within the United Kingdom, including 3710

(22.7%) women, admitted with OHCA secondary to AMI during a 7-year time frame (2010 to 2017). The authors found that compared with men, women were older and more likely to be White. Cardiogenic shock was more common and the time from the emergency call to hospital arrival was longer for women. Women additionally were less likely to be seen by a cardiologist and less likely to receive guideline-directed medical therapies. In-hospital mortality was higher in women compared with men, which remained significant after multivariable adjustment. Similarly, even after adjustment, women were noted to have lower odds of receiving coronary angiography and revascularization, driven by lower use of coronary artery bypass graft surgery. The strengths of this study arise from the authors' ability to study a large sample of patients from a rich, reputable database. The authors were able to detect sex-related differences in outcomes after OHCA after adjustments for patient characteristics, clinical presentations, and in-hospital management. The implications of the presented results need to be discussed in the context of the current state of knowledge of sex-related differences in cardiovascular disease and OHCA.

Prior studies have reported mixed results for sex-related differences in mortality outcomes after OHCA.<sup>6-8</sup> The first systematic review and meta-analysis evaluating the role of patient sex in OHCA outcomes included 13 observational studies. This study found that women had increased odds of survival to hospital discharge or 1 month after the event compared with men, which remained true after multiple sensitivity analyses, including limiting analysis to studies of OHCA of cardiac origin only.<sup>6</sup> However, there was no analysis of in-hospital interventions. Studies that followed argued otherwise. Lei et al<sup>7</sup> analyzed data

See also page 1608

from 33 studies looking at a primary outcome of survival from OHCA to hospital discharge. They found that survival to hospital discharge was significantly lower for women than for men. This study additionally indicated that women generally received fewer interventions after OHCA, such as percutaneous coronary intervention, coronary angiography, and targeted temperature management. The authors postulated that these differences in medical care during patient hospitalization may explain why they saw no significant sex difference in survival at hospital admission but lower survival for women at hospital discharge.<sup>7</sup> In another systematic review and meta-analysis of 14 observational studies of patients with OHCA, Parikh et al<sup>8</sup> also found that female sex was associated with significantly higher in-hospital or 30-day all-cause mortality after OHCA. With respect to sex-related differences in the management of acute coronary syndrome, women are less likely to receive guideline-directed medical therapy, coronary angiography, and timely reperfusion.<sup>9</sup>

The study by Dafaalla et al has several strengths and not only confirms previous observations but also extends our knowledge and understanding of sex differences in outcomes after OHCA secondary to AMI. First, it provides population-based data confirming that in-hospital mortality was higher for women with OHCA secondary to AMI compared with men. Second, the authors performed an analysis of in-hospital interventions and addressed sex-based differences in receiving state-of-the-art treatment between the sexes that may result in worse outcomes in women. Notably, and similar to prior studies, Dafaalla et al found a tendency toward a less aggressive approach in women hospitalized with OHCA secondary to AMI: women were less likely to be seen by a cardiologist or to receive evidence-based medical therapies and had lower odds of receiving coronary angiography and revascularization.<sup>5</sup> Third, the authors found that there was a trend toward improvement in the use of coronary angiography and percutaneous coronary intervention in

women during the study period. Fourth, they propose strategies aimed at minimizing treatment bias and improving communication between female patients and physicians to close the gap.

In addition to the potential influence of differences in health care delivery, many questions remain as to whether sex-related differences in mortality outcomes after OHCA could be biologic in nature as well. Multiple findings in the study by Dafaalla et al suggest that women with OHCA have more significant effects of long-standing hypertension, including an increased prevalence of baseline chronic kidney disease and strokes, both of which could also suggest less well controlled hypertension. Together with advanced age, these findings suggest that women with OHCA may have more significant left ventricular hypertrophy as a potential substrate for fatal arrhythmias. Compared with their male counterparts who historically have more coronary artery disease, this leads to a different cause of sudden cardiac death, which could explain some of the differences seen. Regardless of the acute cause, the concept that women have a unique substrate for sudden cardiac death could also relate to hormonal differences in rhythm conduction. It is well recognized, for instance, that hormones affect conduction at the cellular level, particularly ventricular repolarization (QTc interval), through modification of potassium channels.<sup>10</sup> This also raises the question of other differences in care after OHCA in the use of implantable cardioverter-defibrillators and overall long-term outcomes.

In summary, there are increased efforts to improve our understanding of sex-dependent risks in the care of women with heart disease. The study of Dafaalla et al significantly contributes to the current understanding of sex-related differences in the outcomes and management of OHCA secondary to AMI. To optimize the health care delivery for women with cardiovascular disease, a concentrated effort to improve current approaches and minimizing biases is needed and should include policymakers,

educational programs, participation of professional societies, and media campaigns. Future research similarly should address the biology of sex differences and effects of sex-specific risk factors (eg, pregnancy and pregnancy complications, menopause, and hormone therapy, among others). Finally, it remains unclear whether sex differences persist and affect long-term outcomes after hospital discharge from OHCA. These focused efforts may minimize the negative impact of female sex on surviving AMI presenting with OHCA.

### POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

**Kathleen A. Young, MD**  
**C. Charles Jain, MD**

Department of Cardiovascular Medicine  
Mayo Clinic  
Rochester, MN

**Vesna D. Garovic, MD, PhD**

Division of Nephrology and Hypertension  
Mayo Clinic  
Rochester, MN

**Grant Support:** R01HL136348 (V.D.G.).

**Correspondence:** Address to Vesna D. Garovic, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905) ([garovic.vesna@mayo.edu](mailto:garovic.vesna@mayo.edu); Twitter: [@GarovicVesna](https://twitter.com/GarovicVesna)).

### REFERENCES

1. Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet*. 2021;397(10292):2385-2438.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
3. Blom MT, Oving I, Berdowski J, van Valkengoed IG, Bardai A, Tan HL. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. *Eur Heart J*. 2019;40(47):3824-3834.
4. Vogelsong MA, May T, Agarwal S, et al. Influence of sex on survival, neurologic outcomes, and neurodiagnostic testing after out-of-hospital cardiac arrest. *Resuscitation*. 2021;167:66-75.
5. Dafaalla M, Rashid M, Van Spall H, et al. Women are less likely to survive AMI presenting with out-of-hospital cardiac arrest: a nationwide study. *Mayo Clin Proc*. 2022;97(9):1608-1618.
6. Bougouin W, Mustafic H, Marjon E, et al. Gender and survival after sudden cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2015;94:55-60.
7. Lei H, Hu J, Liu L, Xu D. Sex differences in survival after out-of-hospital cardiac arrest: a meta-analysis. *Crit Care*. 2020;24(1):613.
8. Parikh PB, Hassan L, Qadeer A, Patel JK. Association between sex and mortality in adults with in-hospital and out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2020;155:119-124.
9. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133(9):916-947.
10. Zeitler EP, Poole JE, Albert CM, et al. Arrhythmias in female patients: incidence, presentation and management. *Circ Res*. 2022;130(4):474-495.