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EDITORIAL COMMENT

# Female Sex and Acute Heart Failure Predict Mortality Following Acute Coronary Syndrome*

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Sex differences in acute coronary syndrome (ACS), in particular among patients presenting with ST-segment elevation myocardial infarction (STEMI), have been well-documented.[1] Acute heart failure is a strong predictor of mortality among patients presenting with ACS and has been shown to be more prevalent in women presenting with STEMI.[2] However, sex differences in acute heart failure and mortality in patients presenting with ACS remain largely unknown. The paper by Cenko et al[3] in this issue of *JACC: Advances* helps fill some of the gaps using a retrospective study of 87,812 patients in the International Survey of Acute Coronary Syndrome (ISACS Archives) including 35.2% women and 28.7% patients presetting with acute heart failure.

Studies indicate that women presenting with ACS have a higher 30-day mortality risk than men, in part related to longer time to reperfusion, lower rates of percutaneous coronary intervention, and lower rates of evidence-based medical therapy at discharge.[4] Cenko et al[3] extend these prior results by demonstrating that female sex is associated with 1.43-fold higher risk of 30-day mortality independent of age, comorbidities, and delivery of care. This study also shows that acute heart failure was the strongest predictor of mortality and independently associated with 6-fold higher 30-day mortality which is higher than that reported in other cohorts.[2]

In this issue of *JACC: Advances*, Cenko et al[3] also demonstrated important sex differences in acute heart failure and 30-day mortality based on the type of ACS (STEMI vs non-ST-segment elevation acute coronary syndrome); whereas, in a prior study published in JACC 2019, Cenko et al[5] focused on sex differences in acute heart failure after STEMI. When stratified by type of ACS, mortality at 30 days was 1.65-fold higher in women presenting with STEMI and 1.18-fold higher in women presenting with Non-ST-segment elevation acute coronary syndrome compared to men. Women with STEMI had 1.24-fold higher risk of acute heart failure compared to men but the risk of acute heart failure did not differ between women and men with NSTE-ACS. Delay in presentation is an important predictor of acute heart failure in patients presenting with ACS. However, this study demonstrated that the incidence of acute heart failure in STEMI was persistently higher in women compared to men regardless of time to presentation. This higher risk of acute heart failure in women presenting with STEMI regardless of time to presentation may provide insight into the sex differences in STEMI mortality that warrants further investigation. Furthermore, women were more likely than men to have reduced left ventricular ejection fraction (LVEF) after STEMI, whereas they were less likely than men to have reduced LVEF after NSTE-ACS. The reduced LVEF may account for the worse mortality in women presenting with STEMI that was may not be accounted for by the presence of acute heart failure on presentation.

Female sex was found to be a predictor of mortality independent of the presence of acute heart failure on ACS presentation. These findings suggest that there are mechanisms beyond the presence of acute heart

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failure on ACS presentation that result in higher mortality in women that merits further investigation. One potential explanation evidencing further investigation is etiology of myocardial infarction. Data on the procedural outcomes are lacking, however in additional analysis, Cenko et al[3] found that among STEMI patients with acute heart failure a large proportion of women (41.5%) did not receive reperfusion therapy which raises an important question on differences in the underlying pathophysiology in women presenting with STEMI. Women have been shown to a have higher risk of myocardial infarction with no obstructive coronary artery disease such as plaque rupture/erosion, coronary vasospasm, emboli, and myocardial infarction with no obstructive coronary artery mimickers such as takotsubo cardiomyopathy, myocarditis, and non-ischemic cardiomyopathy that do not warrant reperfusion therapy and are associated with poor outcomes.[6,7] Another explanation may be the type of acute heart failure on presentation. Women were more likely to present with heart failure with preserved ejection fraction post-myocardial infarction, whereas men presented with heart failure with reserved ejection fraction. The limited therapy options for heart failure with preserved ejection fraction may also account for the discrepancies in outcomes and mortality. Furthermore, there are women-specific risk factors such as menopause and adverse pregnancy outcomes that have been demonstrated to increase cardiovascular disease and mortality that need to be further investigated to provide better insight into play a role in outcomes after acute myocardial infarction.

As outlined by the authors, there are limitations given the observational nature of the study including inability to exclude residual confounding. However, one of the main limitations of the manuscript is the lack of sex-specific comparisons which the authors state was not performed because acute heart failure is one of the mediators of the effects of ACS on mortality. In a similar publication using the same cohort focused on sex differences in acute heart failure after STEMI, Cenko et al[5] reported that women with new heart failure had 1.29-fold higher 30-day mortality than their male counterpart. This analysis, particularly in the NSTE-ACS group, would have allowed us to better understand sex differences and the contribution related to heart failure on presentation on mortality.

In summary, this study demonstrates that there are important sex differences in acute heart failure presentation and 30-day mortality that differ by type of myocardial infarction. Although women post-STEMI are at higher risk of presenting with acute heart failure, female sex was found to be a predictor of mortality independent of acute heart failure. Further research is needed to better understand how the presence of acute heart failure mediates mortality by type of myocardial infarction. Moreover, the results of this study emphasize the importance of sex-specific analyses to further understand sex disparities in women presenting with ACS.

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**KEY WORDS** acute heart failure, acute myocardial infarction, female sex