Sex, Myocardial Infarction, and the Failure of Risk Scores in Women

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CVD is the leading cause of death in the United States, accounting for one in every three deaths. Annual CVD prevalence and mortality remains higher in women than men, a trend that has persisted for decades. Over the last decade, advances have been made in our understanding of sex (biology) and gender (sociocultural) differences in CVD symptom manifestation and pathophysiology, contributing to better diagnostic and treatment modalities for CVD in women. Despite these advances, female CVD mortality rate remains disproportionately high and the root causes underlying this inequity remain speculative.

In this issue of Journal of Women’s Health, de-Miguel-Balsa et al. demonstrate that women with ST segment elevation myocardial infarction (STEMI) have higher hospital mortality than men, a finding that is consistent with prior literature. When they adjust excess mortality in women for baseline risk using the GRACE risk scoring system, women continue to have unexplained higher mortality rates. However, when they adjust using the Killip or TIMI risk scoring system, the unexplained additional risk in women disappears. This finding highlights the need for further investigation in comparing the variables of the three aforementioned risk-scoring systems to elucidate the strongest mortality risk factors in women with STEMI.

As shown in Table 1, the Killip scoring system is comprised of only two variables: severity of heart failure and systolic blood pressure. Heart failure is an important risk factor because, in women, heart failure as opposed to coronary heart disease (CHD) is more commonly the first manifestation of cardiovascular disease. In contrast, in men, CHD is often the first manifestation of CVD. Heart failure is recognized as an essential variable in risk stratification of women as it is included in all three risk-scoring systems with the TIMI and GRACE systems using the Killip class as a variable. In addition, however, the impact of heart failure as a risk factor for STEMI mortality brings up the point that relatively less is known regarding heart failure with preserved ejection fraction (HFpEF), which is more common in women, and therefore specific strategies to investigate and understand HFpEF in women are urgently needed.

The GRACE system has three unique variables when compared with TIMI: cardiac enzymes, creatinine, and cardiac arrest at admission. These variables may be responsible for some of the sex-specific differences in mortality by either raising female risk or lowering male risk. The most commonly used cardiac enzymes in risk stratification, such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT), have been shown to have significantly different mean concentrations between men and women, suggesting the need for establishment of sex-specific ranges. In a 2015 study, Shah et al. found that when the current practice threshold for cTnI of 50 ng/L was utilized, men were twice as likely as women to have a diagnosis of myocardial infarction (MI) despite a similar proportion of men and women reporting chest pain and demonstrating electrocardiographic changes. Using a high sensitivity assay with sex-specific diagnostic thresholds (34 ng/L for men, 16 ng/L for women) doubled the diagnosis of MI in women, such that the diagnosis proportion was now similar to the proportion for men. Subsequently, they found that the women identified using high sensitivity cTnI sex-specific thresholds had the highest risk of mortality or recurrent MI, indicating that these women can potentially greatly benefit from reclassification and treatment.

Sex-specific differences in cardiac enzymes by gender can be partially explained by the finding that troponin levels correlate with left ventricular mass, and women have smaller left ventricular mass regardless of adjustment for height or body surface area. Furthermore, while women are less likely to have biomarker evidence of cardiac myocyte injury and/or necrosis, they have been shown to have higher levels of other markers that are emerging in risk stratification in acute coronary syndrome (ACS) such as C-reactive protein and brain natriuretic peptide; such differences in biomarker levels suggest differences in the pathophysiology of ACS in men versus women, where the former involves atherosclerotic plaque rupture and thrombus formation while the latter more commonly involves small vessel coronary disease, vascular inflammation, or congestive heart failure. Overall, given that women are less likely to reach the current troponin threshold for diagnosis of ACS, those women who do likely have a more severe disease process and suffer a larger MI.

Similar to differences in cardiac enzyme levels, sex-specific differences in circulating creatinine levels have been discussed in the literature. It is estimated that >98% of creatinine comes from muscle, where it is secreted into the serum, and

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subsequently excreted by the kidneys. Higher creatinine levels can result from either higher muscle mass or worsening renal function. Women in general have less muscle mass and therefore lower baseline serum creatinine. Barthelemy et al., among others, have shown that women presenting with STEMI have lower mean creatinine clearance than men presenting with STEMI. Therefore, in women and men that are matched to the same creatinine level, women have worse kidney function. Decreased kidney function is associated with higher risk of recurrent CHD events and mortality from CHD and all causes. A better method of risk stratification may be to use estimated glomerular filtration rate (eGFR) rather than serum creatinine since the most common equations, the Cockcroft-Gault and the Modification of Diet in Renal Disease equations, take gender into account in the calculation of GFR. Furthermore, new studies should be carried out to determine whether previously observed non-CVD specific elevation of circulating cTnT in patients with chronic kidney disease or reduced GFR is maintained with the application of new high sensitivity assays in comparison to cTnI, which previously demonstrated better correlation to true myocardial injury in the same patient cohorts.

In terms of sex differences in cardiac arrest, several studies have shown that women who suffer a cardiac arrest have higher survival to hospital admission but worse prognosis in the hospital. It is speculated that the reason women may have increased survival to the hospital is that women are more likely to activate vagal compensatory mechanisms in response to abrupt coronary occlusion, which have beneficial antiarrhythmic effects. However, women are thought to have worse prognosis in the hospital in part because they present more often in asystole or pulseless electrical activity. The higher prevalence of nonshockable rhythms could be secondary to lower incidence of bystander cardiopulmonary resuscitation, an intervention that has been shown to maintain ventricular fibrillation, as well as cardiac arrests due to noncardiac etiologies in women compared with men. Nonshockable rhythms prevent defibrillation and further therapy. Overall, women who present with cardiac arrest at admission are at higher risk for mortality than men who present with cardiac arrest at admission.

The sex differences in cardiac enzymes, creatinine, and cardiac arrest at admission that are utilized in the GRACE scoring system but not in the Killip and TIMI scoring systems contributes to our understanding regarding why the GRACE scoring system identifies the excess mortality in women with STEMI and provides insight into sex-specific risk stratification.

Specifically, because the GRACE score correctly identifies the higher mortality experienced by women with STEMI, and includes variables that vary significantly according to sex, these data identify areas of focus for both investigation and guideline formation. Further sex-specific investigation into high sensitivity cardiac troponin (cTnI or cTnT), novel biomarkers of relevance to ischemic heart disease and sudden death is ongoing and needed. Guidelines whereby clinical chemistry laboratory reporting stratifies troponin and creatinine according to male and female ranges should be tested and established. It is clear that current risk scores, which are based on ACS thresholds determined in predominantly male-based populations, do not work well for predicting risk in women. These data combined with the disparate CVD outcomes in women call for the further development and use of sex-specific biomarker ranges and risk stratification tools in order to enhance the diagnosis, treatment, and follow-up in female populations. Lastly, while risk scores are particularly useful for quality assurance purposes, they have demonstrated strong discriminatory utility in understanding outcomes following percutaneous intervention at the individual level both in the short and long term and therefore should be maintained and evolved with new sex-specific criteria.

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