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

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CARDIOVASCULAR DISEASE (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.¹ 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.^{2,3}

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.⁴ 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.^{5–7} 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.⁸ 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.⁹ 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.¹⁰

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.^{11,12} 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 suggests 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.¹³ 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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TABLE 1. RISK SCORING SYSTEM COMPONENT VARIABLES

<i>Killip</i> ⁶	<i>TIMI</i> ⁷	<i>GRACE</i> ⁵
Severity of heart failure (presence of rales)	Killip class	Killip class
Systolic blood pressure	Systolic blood pressure	Systolic blood pressure
	Age	Age
	Heart rate	Heart rate
	Anterior STE or LBBB	ST segment deviation
	DM/HTN or angina	Creatinine
	Weight (if <67 kg)	Cardiac arrest at admission
	Time to rx >4 hours	Elevated cardiac enzyme levels

DM/HTN, diabetes mellitus/hypertension; GRACE, Global Registry of Acute Coronary Events; LBBB, left bundle branch block; rx, therapy; ST, ST segment; TIMI, thrombolysis in myocardial infarction.

subsequently excreted by the kidneys.¹⁴ 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.¹⁵ 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.¹⁶ 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.¹⁷ 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.^{18–20}

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.^{21–23} 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.²³ 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.²² 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.²⁴

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References

1. Mozaffarian D, Benjamin EJ, Go AS, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—

- 2015 update: A report from the american heart association. *Circulation* 2015;131:e29–322.
2. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: Evolving knowledge. *J Am Coll Cardiol* 2009;54:1561–1575.
 3. Mieres JH, Gulati M, Bairey Merz N, et al., American Heart Association Cardiac Imaging Committee of the Council on Clinical Cardiology, Cardiovascular Imaging and Intervention Committee of the Council on Cardiovascular Radiology and Intervention. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: A consensus statement from the american heart association. *Circulation* 2014;130:350–379.
 4. de-Miguel-Balsa E, Latour-Pérez J, Baeza-Román A, Llamas-Álvarez A Ruiz-Ruiz J, Fuset-Cabanes, MP. Accessibility to reperfusion therapy among women with acute myocardial infarction: Impact on hospital mortality. *J Womens Health* 2015. [Epub ahead of print]; DOI: 10.1089/jwh.2014.5011.
 5. Granger CB, Goldberg RJ, Dabbous O, et al.; Global Registry of Acute Coronary Events I. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345–2353.
 6. Khot UN, Jia G, Moliterno DJ, et al. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: The enduring value of Killip classification. *JAMA* 2003;290:2174–2181.
 7. Morrow DA, Antman EM, Charlesworth A, et al. Timi risk score for st-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous npa for treatment of infarcting myocardium early ii trial substudy. *Circulation* 2000;102:2031–2037.
 8. Leening MJ, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: Prospective population based cohort study. *BMJ* 2014;349:g5992.
 9. Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase mb mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. *Clin Chem* 2003;49:1331–1336.
 10. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: Prospective cohort study. *BMJ* 2015;350:g7873.
 11. Rosjo H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin t in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol* 2011;108:88–91.
 12. Salton CJ, Chuang ML, O'Donnell CJ, et al. Gender differences and normal left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study offspring cohort. *J Am Coll Cardiol* 2002;39:1055–1060.
 13. Wiviott SD, Cannon CP, Morrow DA, et al. Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: A TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18) substudy. *Circulation* 2004;109:580–586.
 14. Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: The heart and soul study. *Circulation* 2010;121:1295–1303.
 15. Barthelemy O, Degrell P, Berman E, et al. Sex-related differences after contemporary primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Arch Cardiovasc Dis* 2015. DOI: 10.1016/j.acvd.2015.03.002; [Epub ahead of print].
 16. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: The atherosclerosis risk in communities (aric) study. *Am Heart J* 2006;151:492–500.
 17. Kontos MC, Jamal SM, Ornato JP, Tatum JL, Jesse RL, Anderson FP. Comparison of the modification of diet in renal disease and the cockcroft-gault equations for predicting mortality in patients admitted for exclusion of myocardial ischemia. *Am J Cardiol* 2008;102:140–145.
 18. Aksoy N, Ozer O, Sari I, Sucu M, Aksoy M, Geyikli I. Contribution of renal function impairment to unexplained troponin T elevations in congestive heart failure. *Ren Fail* 2009;31:272–277.
 19. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002;106:2941–2945.
 20. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *New Engl J Med* 2002;346:2047–2052.
 21. Pell JP, Sirel J, Marsden AK, Cobbe SM. Sex differences in outcome following community-based cardiopulmonary arrest. *Eur Heart J* 2000;21:239–244.
 22. Karlsson V, Dankiewicz J, Nielsen N, et al. Association of gender to outcome after out-of-hospital cardiac arrest—A report from the International Cardiac Arrest Registry. *Crit Care* 2015;19:182.
 23. Perers E, Abrahamsson P, Bang A, et al. There is a difference in characteristics and outcome between women and men who suffer out of hospital cardiac arrest. *Resuscitation* 1999;40:133–140.
 24. Bawamia B, Mehran R, Qiu W, Kunadian V. Risk scores in acute coronary syndrome and percutaneous coronary intervention: A review. *Am Heart J*. 2013;165:441–450.

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