Reperfusion and Time to Presentation in Women: Too Little Too Late

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Cardiovascular disease remains the leading cause of death for women both in the United States and around the world.[1] The past 3 decades of practice-changing research in prevention, diagnosis, and treatment of cardiovascular disease has been associated with a progressive decline in mortality rates. The rewards of this work have been shared unequally; since 1984, women have continued to have higher annual cardiovascular disease mortality rates than men.[2] After the diagnosis of acute myocardial infarction, mortality rates for women are higher at 1 and 5 years, and women are more prone to developing heart failure and stroke. Women are also at higher risk of complications after coronary revascularization and other cardiac procedures, including higher rates of bleeding and additional adverse events.[3–5]

The blame for the sex-lag in improved cardiovascular disease mortality and outcomes in women compared with men is shared broadly; it includes older age, longer symptom-to-presentation time, lower rates of revascularization, and social and environmental factors as well as biological features specific to women. Recognition and adjustment for these differences often mitigate much of the difference in outcomes but particularly in large-scale studies, an independent effect of sex persists. Moreover, underrepresentation of women in clinical research has likely hindered the full potential of new discovery to be applied to women.[6–8] Although studies across the spectrum of cardiovascular disease during nearly the past 5 decades in patients treated with medical therapy or with coronary revascularization in addition to guideline-recommended medical therapy have been remarkably consistent in reports of sex-based differences in the presentation, diagnosis, treatment and outcomes, the underlying basis for these findings largely remains elusive.[9]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Cenko and colleagues take a step in helping to account for sex-specific biological factors.[10] Within the ISASC-TC (International Survey of Acute Coronary Syndromes in Transitional Countries), a large, prospective, multicenter registry of patients with acute coronary syndromes, 2596 patients with complete clinical and hemodynamic information who underwent primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction (STEMI) between January 2010 and 2016 were evaluated, of whom 673 (26%) were women. Similar to other studies, women in this group were older, with a higher prevalence of comorbidities such as diabetes mellitus, hypertension, and congestive heart failure in comparison to men. Unadjusted mortality was higher in women at 5.9% compared with 2.3% in men, and angiographic analysis revealed the rate of suboptimal thrombolysis in myocardial infarction (TIMI) 0 to 2 flow following reperfusion in women to be higher than in men, 8.0% versus 4.7%. Using a nonparametric balancing strategy by weighting to adjust for differences between women and men, the primary outcome of all-cause mortality at 30 days remained unfavorable for women at 4.8% compared with 2.5% for men. There was also a significant sex difference in post percutaneous coronary intervention TIMI flow 0 to 2, 8.8% versus 5.0% in women and men, respectively (odds ratio 1.83, 95% CI 1.31–2.56).

While there were no differences observed in door-to-balloon time between sexes, median symptom-to-presentation time was significantly longer for women, 280 minutes compared with 249 minutes for men. The authors stratified their outcomes of interest for patients who had delayed time to hospital presentation (≥120 minutes from onset of symptoms) and those who did not, and found that for patients with delayed presentation, mortality was higher for women compared with men (5.5% versus 2.8%), but similar when time to hospital presentation was not delayed (<120 minutes). In contrast, the incidence of suboptimal TIMI flow 0 to 2 was persistently higher in women compared with men, regardless of the time to hospital presentation (9.4% versus 6.3% in those with presentation

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≥120 minutes; 7.9% versus 1.6% in those with presentation <120 minutes from symptom onset). There was also nearly 3-fold higher mortality in women compared with men with TIMI 0 to 2 flow, irrespective of time to presentation. Based on these findings, the authors postulate that delayed presentation and suboptimal postprocedural TIMI flow grade are variables independently associated with increased mortality in women.

Notwithstanding the inability to account for sex differences in the incidence of distal embolization of thrombus, use of aspiration thrombectomy, infarct size, and left ventricular function associated with abnormal TIMI flow and whether assessment of TIMI flow was blinded to sex, this study not only confirms the well-established increased risk and complications that women have following acute myocardial infarction, but also adds to our understanding by suggesting an important mechanistic basis. With thoughtful and thorough analyses using both multivariable logistic regression and inverse probability of treatment-weighted models, the data generated support increasing evidence of microvascular disease and endothelial dysfunction in women, which may be associated with adverse outcomes. A growing literature has developed possible mechanisms for myocardial infarction in the setting of nonobstructive coronary arteries, a syndrome that seems to disproportionately affect women.[11–15] Research has implicated coronary microvascular and endothelial dysfunction, and impaired coronary flow velocity reserve in women. Increasingly, it has been recognized that the prognosis of this syndrome is not as benign as previously thought, and the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation and Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients studies have reported that women without obstructive coronary artery disease continue to have increased rates of cardiovascular disease events.[16–18]

While the present study explores a syndrome at the other end of the spectrum from myocardial infarction in the setting of nonobstructive coronary arteries, namely, atherothrombotic coronary disease manifest as STEMI, the 2 phenomena may be linked by their core finding. The excess mortality in women with STEMI, even adjusting for unfavorable baseline characteristics, could be related to the observed suboptimal procedural success, and associated microvascular dysfunction. The current study, as the authors concede, is unable to establish such causality, but it is noteworthy that while microvascular dysfunction increases with increasing time to reperfusion, a higher incidence of TIMI 0 to 2 flow persisted in women even when symptom onset to presentation (<120 minutes) was not (or less) delayed. In contrast, sex difference in mortality rates was no longer apparent in patients presenting in <120 minutes.

The disadvantage of prolonged time of symptom-onset-to-presentation was 2-fold for women: a greater percentage of women had delayed presentation, and women with delayed presentations had higher mortality than men with delayed presentation. The challenge of timely diagnosis and treatment of STEMI remains, and while the gender gap has improved, it persists, and is costly in terms of survival for women.[19–21] Improving awareness of the prevalence and burden of ischemic heart disease and symptoms of acute coronary syndromes among women should remain an important public health and societal objective. It should not go unnoticed, however, that while only 23.2% of women presented in <120 minutes of symptom onset, only 29.1% of men did so as well, despite the development of systems of care for STEMI across the country and significant improvement in door-to-reperfusion times.[22]

The implications of sex-based differences in endothelial vulnerability to ischemia and atheroembolism are numerous. Yet to be determined are the correct pharmacological and interventional adjustments necessary to achieve the best individualized treatments for both women and men. The choices of upstream and intraprocedural antithrombotic and antiplatelet therapy, percutaneous thrombectomy, distal embolic protection, and other therapies for the prevention or treatment of no-reflow during percutaneous coronary intervention will likely be influenced by sex. Importantly, this reinforces the growing clamor for enrollment of more women in clinical research trials, and to power such studies to allow for appropriate sex-specific analysis for questions such as response to drug or interventional therapies, rather than to rely on post-hoc subgroup analysis.[23]

The findings of Cenko and colleagues represent another advance in furthering our understanding of the mechanisms of vulnerability in women with STEMI and highlight the ongoing need to accurately account for biologic factors specific to women. And while we have seen progress in the past 2 decades, much work remains in understanding the anatomic and physiologic features that predispose a higher burden of cardiovascular mortality and complications on women. Furthermore, we must continue to work so that women (and men) are equipped with the knowledge and disease awareness to understand the importance of time to treatment when acute myocardial infarction is suspected and present to the hospital as soon as possible to ensure the best outcomes. Finally, only when clinical studies and large-scale trials routinely respond to the limitations of the underrepresentation of women will we able to apply our growing evidence and realize its full potential.

Disclosures

None.

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