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REPLY: Sex Differences in Outcomes of LVAD Patients Bridged to Transplant: The Problem of Selection Bias



We recently reported the results of our analysis of sex-related differences in the use and outcomes of left ventricular assist devices (LVADs) as bridge to transplantation using the United Network for Organ Sharing (UNOS) registry (1). We found that women receiving LVAD support had lower rates of heart transplantation and increased risk of waitlist mortality using a propensity-matched cohort.

We thank Dr. Wehbe and colleagues for their interest in our study. We agree that there could be other confounding factors that might have been unaccounted for in this registry analysis and potentially have contributed to the differences observed in waitlist outcomes between female and male LVAD recipients. Variables in the UNOS registry are obtained at the time of transplant listing and heart transplantation, as opposed to LVAD implantation. As such, these variables may not fully reflect the level of sickness or end-organ dysfunction at the time of LVAD implantation. For example, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile at the time of LVAD implantation is not available in the UNOS registry. Despite these limitations, we included all relevant variables available in the UNOS registry in an effort to balance the risk between female and male patients.

Of particular importance was the higher incidence of human leukocyte antigen sensitization in female LVAD patients, which is a challenge we face in clinical practice and could certainly contribute to lower rates of transplantation observed in female LVAD patients. We have successfully desensitized LVAD patients using intravenous immunoglobulin, plasmapheresis, and monoclonal antibodies targeting CD20; however, data regarding this approach remain limited.

We found no difference in device complications between female and male patients as determined by UNOS Status upgrade; however, there was a significant increase in waitlist mortality in female LVAD patients, as suggested by previous studies. We agree with the authors that there is likely no biologically plausible explanation.

However, in practice women are often referred to advanced therapies later than men and are less likely to be transplanted (2,3). We also know that women are less likely to receive diuretics, anticoagulants, and device therapy (4). Multiple studies have demonstrated significant differences in the use of heart replacement therapies (5,6). These differences

were once again observed in our analysis and require explanation.

Although this may represent selection bias, it also indicates gender bias. It highlights the need for the heart failure community and cardiology community at large to realize the consequences of delayed referral and inequities in our current health care systems. Our findings emphasize the need for us to reframe our “typical clinical decision making” in which women are sicker at the time of listing.

We concur with Dr. Wehbe and colleagues on the need for studies focusing on destination therapy patients alone to investigate sex differences in LVAD outcomes. It also remains to be seen how the new UNOS heart allocation system will affect transplantation strategies and these differences in outcomes between men and women.

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Personalized Medicine



Women in Heart Failure Clinical Trials, a Must!

We read with great interest the paper by Merrill et al. (1) reporting that spironolactone is associated with a reduction in all-cause mortality in women but not in

men with heart failure with preserved ejection fraction, enrolled in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial (2). The authors should be congratulated for exploring differences in clinical response to drugs between men and women. Their analyses highlight the importance of stratified randomization by sex and sample sizes large enough to make conclusions in both men and women.

The random assignment of treatment is an essential feature of randomized clinical trials (RCT) that maximizes comparability between treatment groups. Subgroup analyses are often performed to estimate the effect of the drug based on specific characteristics, such as patient sex. However, subgroup analyses have limitations including not adjusting for covariates. Because randomization is not usually stratified by sex, women and men, despite being randomized to treatment, may not have comparable clinical characteristics. In fact, in stratifying by sex, Merrill et al. (1) uncovered how women and men had a significantly different clinical profile. Women were older, with fewer comorbidities (i.e., coronary artery disease and atrial fibrillation), but with higher blood pressure and body mass index. Such imbalances between women and men highlight the need for randomization stratified by sex.

Merrill et al. (1) performed appropriate analyses with sex-specific hazard ratios for both placebo and treatment groups and multivariate models adjusting for the differences between men and women including age and comorbidities. The inclusion of the sex-by-treatment interaction in the multivariate model was essential in capturing the modifying effect of sex that otherwise would have been ignored (2). Indeed, the sex-by-treatment interaction approach led to detect a benefit in all-cause mortality only in women. This hypothesis-generating analysis imposes a reflection on the potential sex-specific mechanisms underlying the effect of spironolactone, and more importantly, the use of this drug in men.

Under-representation of women in RCTs is unfortunately common, especially in heart failure trials (3), therefore RCTs are commonly underpowered to detect any difference in drug efficacy. Even though 51% of women in TOPCAT is fairly representative of the prevalence in heart failure with preserved ejection fraction populations (4), the favorable results in women could have been caused by enrollment of healthier women than men. In fact, we cannot rule out screening bias whereby the process excludes sicker women because the number of individuals not enrolled for failure to meet study criteria is not reported. Even more, we cannot exclude that women

are less willing to participate in RCTs because of gender-related (i.e., psycho-socio-cultural) factors, so their health vulnerability might be under-evaluated (5).

Overall, this paper provides an excellent example of how the methodologic limitations of reporting sex-subgroup analyses with unadjusted forest plots can be mitigated and how informative can a sex-based analysis be. Personalized medicine is the upcoming opportunity for clinicians and researchers, and we believe that the integration of sex in the analyses and design of trials should be vigorously pursued.

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On the Way to Accurately Evaluate Cardiac Function in Patients With Heart Failure



We read with great interest the paper by Savarese et al. (1) showing us a new potential use for left ventricular ejection fraction (EF) as a predictor of heart failure (HF) progression in daily clinical