

## EDITORIAL COMMENT

# Sex Does Matter

## Risk of Stroke in LVAD Recipients\*



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Advanced heart failure therapies including both heart transplant and left ventricular assist devices (LVADs) are underutilized in women. Proposed reasons for this include delayed recognition of advanced heart failure symptoms, comorbidities affecting eligibility, and concerns around the willingness of women to undergo advanced therapies.<sup>1-3</sup> As technological improvements continue to decrease the burden of hemocompatibility-related adverse events (AEs),<sup>4,5</sup> it is paramount to identify the reasons behind the underutilization of this therapy in women and tailor therapy based on sex-related differences.

Earlier generations of LVADs have had variable results related to sex-based differences in AEs.<sup>6,7</sup> Even with the current generation of devices, LVAD-related AEs remain a significant burden for patients contributing to morbidity and mortality in >50% of patients. Older studies suggested that women are at a higher risk of major bleeding, right ventricular failure, stroke, and post-LVAD mortality, particularly earlier post-implant.<sup>8</sup> However, more contemporary data from the MOMENTUM 3 trial showed no differences in survival between men and women at 2 years post-implant, though women make up approximately 20% of the study population.<sup>9</sup>

A common and devastating LVAD-related AE, stroke, is the primary cause of death amongst LVAD recipients; it occurs in up to 13% of patients within

the first year post-implant. Hemodynamic changes that predispose to the stroke risk in LVAD patients include endothelial damage and activation of the coagulation cascade due to continuous flow, as well as dysfunction in the syntheses of fibrinolytic substances contributing to hypercoagulability.<sup>10</sup>

Specific to sex, stroke risk has been frequently described as being higher in females when compared to males with the leading proposed mechanisms including hormonal sex-related differences. It has been noted that when a female has traditional modifiable risk factors for stroke such as hypertension, they are more likely to have a stroke when compared to male.<sup>11</sup> Specific to LVAD therapy, a prior INTERMACS analysis found female sex to be a preimplant predictor of stroke implanted with a LVAD between 2012 and 2015.<sup>12</sup> Although the role of estrogen's influence on stroke risk remains unclear, estrogen can influence both coagulability and endothelium function along with nitric oxide formation.

In this issue of *JACC: Advances*, Zook et al<sup>13</sup> performed a retrospective analysis of patients who underwent LVAD placement between 2010 and 2019 using National Inpatient Sample data. They examined patients who experienced a stroke during their sentinel hospitalization and compared their clinical characteristics and outcomes over a 10-year period. The study population consisted of 35,820 LVAD patients above the age of 18 years with mean age of 57 years with 23% of encounters being women and 77% being male.

There were significant differences in baseline characteristics: men were older (mean age of 59.3 years vs 50.7 years) with more comorbidities (diabetes mellitus, hypertension, atrial fibrillation, renal failure, hyperlipidemia), and the women had a higher incidence of hypothyroidism and significantly lower income class (23% vs 18%).

The authors found that the incidence of stroke in all patients was 6.1%. This result, which is

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significantly less than other contemporary studies, may be explained by a focus on the immediate post-operative period. The incidence of overall stroke was similar between both men and women. Despite implanted women being younger and with less comorbidities, they were more likely to experience a hemorrhagic stroke compared to men (2.6% vs 1.8%,  $P = 0.036$ ). Proposed reasoning includes sex-hormone-related influences on hemocompatibility along with sex-related differences on the endothelial activation system on anticoagulation management. Consistent with prior studies, those who experienced a stroke had a higher mortality compared to those who did not (39.0% vs 9.6%).

Zook et al<sup>13</sup> should be applauded for contributing this important analysis, which demonstrated a higher incidence of hemorrhagic stroke and trend towards higher stroke rates in females. This should further motivate the community to consider a patient-focused driven anticoagulation and management strategy with sex as a pertinent risk factor. Major strengths of this study include a large U.S.-based population and, thus, its applicability to our patient population. In addition, there was a granular evaluation of the sex-based characteristics between those patients who experienced a stroke or not. Limitations of this study include its retrospective nature as well as the lack of identification

of LVAD device types, as there are varying stroke rates between the different continuous flow LVADs.

All in all, stroke remains the leading cause of mortality in LVAD recipients. However, with the recent data from MOMENTUM 3, the current centrifugal flow LVAD demonstrated improvement in both short- and long-term survival along with decreasing burden of LVAD-related AEs, including stroke. However, similar to the data from Zook et al<sup>13</sup> the MOMENTUM 3 data still demonstrated a higher incidence of stroke-related complications in females compared to males (absolute risk reduction: 1.71). Although Zook et al<sup>13</sup> join a growing body of literature to further explain and understand sex-based risk factors, it is paramount that we continue to investigate why sex does indeed matter in our LVAD recipients.<sup>14</sup>

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