Sex Differences in the Care of Patients With Advanced Heart Failure

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The patient was a frail-appearing woman slumped in a wheelchair, surrounded by her 3 children. Her head tilted slightly in greeting, but beyond her rapid and deep respiratory effort, she was too weak to move. She had been discharged 3 days previously from an outside hospital where she was confined for 3 weeks and had arrived at the academic medical center for a posthospital visit. The recent admission followed 4 others in the previous 6 months. Now, she was living at home in hospice care. The family arrived that day hoping that, as they heard from the previous 6 months. Now, she was living at home in hospice care. The family arrived that day hoping that, as they heard from a church friend, the heart failure (HF) specialist might be able to help. The patient was more accepting, saying, “The doctors told me that I am dying, and there is nothing that they can do. I am at peace; I don’t want to be a bother to no one.”

There are 5.7 million patients with HF in the United States over half of whom are women. Each year 33 700 women will die from this disease, representing 58% of all annual HF deaths.1–3 Although women and men are equally likely to have HF, women are more likely to die from it. Despite these facts, many Americans think that men are at greater risk for heart disease and that women are more likely to die from breast cancer.

Why is the risk of HF in women underappreciated? The substantial numbers of women with HF with preserved ejection fraction (HFrEF) may be a contributor. It is known that HF with reduced EF (HFrEF) accounts for only a portion of patients with symptomatic HF. In a cohort of patients from Olmsted County, MN, HFrEF accounted for only 57% of patients with HF, whereas 43% of patients had an ejection fraction of >50%. Patients with HFrEF were more likely women (69%) and almost half of them were above the age of 80.4 Subsequent surveys have also demonstrated an increased frequency of HFrEF in women compared with men where women comprise between 71% and 75% of patients with HFrEF.5,6

HF Mortality
It may be perceived that women with HF have a lower risk of mortality compared with men. Epidemiological studies, including National Health and Nutrition Examination Survey (NHANES-1) and Framingham, reported that women diagnosed with HF have higher expected survival than men.7 This has been recently challenged as it has been pointed out that these cohorts included both patients with HFrEF and patients with HFrEF. In the Studies of Left Ventricular Dysfunction (SOLVD) clinical trial, men and women aged between 21 and 80 years with an EF of <35% and symptomatic HF received enalapril versus placebo. In this cohort, women had a greater 1-year mortality rate, 22% when compared with 17% in men (P=0.05). This may better represent sex differences in mortality in HFrEF.8 The SOLVD patient population differed from previous epidemiological studies because an assessment of left ventricular function was required on entry. It is thus probable that women followed in the earlier epidemiological studies, with diagnosis of congestive heart failure being made on symptoms without an assessment of left ventricular function, had a higher incidence of diastolic dysfunction. This may account for their demonstrated survival advantage. In addition, women in SOLVD had a higher incidence of coronary disease than did the women in Framingham or NHANES-1,7 which may have contributed to their worse prognosis.

Both women and men with HFrEF who have advanced symptoms benefit from evaluation by an advanced HF specialist for consideration of therapy, such as mechanical circulatory support (MCS) and cardiac transplantation. As symptoms worsen, physical disability sets in and hospital admissions mount, and their lives may depend on it. However, referral of appropriate patients is underused in both men and women with HFrEF.9 Certain clinical indicators signify increased mortality risk, such as low New York Heart Association functional class, intolerance to evidence-based HF. Women with HF face a greater uphill battle because they are less likely than men to be referred for cardiology specialist management and are more commonly managed by their primary care physician despite the severity of their symptoms.7

Cardiac Transplantation
Cardiac transplantation is currently the most successful therapy for selected patients with end-stage HF. Each year, ≈2200

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heart transplants are performed in the United States with the major limitation to broader use being inadequate donor supply. Women represent between 19% and 27% of annual adult heart transplant recipients. Data from the Scientific Registry of Transplant Recipients demonstrate that of the 2143 adults who underwent heart transplantation in 2013, 27% were women. The proportion of female recipients has been rising steadily, increasing by 27% between 2008 and 2013, compared with only a 12% increase in men during the same period.

Adult female transplant recipients tend to be younger than men. In 2014, 37% of the women who underwent transplantation in the United States were <50 years of age compared with 26% of the men. Of the 380 recipients who were ≥65 years of age, 16% were women compared with 22% men. These trends may be related to known sex differences in the causes of HF; however, as with other types of cardiovascular disease, questions on sex-specific differences in recognition, referral, and refusal on the part of the patient arise. Furthermore, transplant stability, donor availability, and transplant outcomes may be affected by immunologic challenges and sensitization, which are more prevalent in women because of pregnancy.

**Mechanical Circulatory Support**

Because of the limitations of heart transplantation, MCS has emerged as an alternative treatment for end-stage HF. Unlike early ventricular assist devices (VADs) that required confinement in the intensive care unit, currently used VADs are fully implantable and are powered by an external battery source. The VAD allows patients with end-stage HF to return home and resume normal activities while on support. VADs are used in 2 different scenarios: in patients who are awaiting heart transplantation (bridge-to-transplant [BTT]) and as final (or destination) therapy for those ineligible for heart transplantation.

Early on, application of VAD technology was limited by the large size of the pump (3.74 pounds) allowing for implantation only for patients with a body surface area (BSA) >1.5 m². Because women generally have a smaller BSA and weight, it is not surprising that the early clinical trials only enrolled 22% women. With technological advances, however, VADs have become smaller and more durable. Because of decreased adverse events and positive outcomes, VADs are increasingly being implanted permanently (ie, as destination therapy). Despite the smaller size of newer VADs, women continue to receive fewer VADs than men and remain under-represented in clinical trials. In the HeartMate II BTT trial, only 22% of patients were women, and in the HeartWare Ventricular Assist Device (HVAD) ADVANCE BTT trial, only 28% of patients were women. In the HeartMate II destination therapy trial, there were 19% women in the treatment arm and 8% in the control arm.

Outside of clinical trial experience, all patients receiving Federal Drug Administration–postapproved VADs are included in a national registry that is designed to evaluate outcomes in MCS. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) provides a more contemporary look at the use of VADs. Among the INTERMACS cohort from June 2006 until March 2010, only 21% were women, and they were more likely to get the newer, smaller device compared with the older, larger one.

**Outcomes of MCS**

Differential outcomes may be posited to explain why women are less likely than men to receive VADs, but this is not the case. Women have an equal survival benefit compared with men after VAD implantation. In the HeartMate II BTT trial, survival was similar for men and women. Men were more likely to be successfully bridged to transplant (M=55% and W=40%; P=0.001), and therefore, not surprisingly, women were supported for a longer period of time (M=184 versus W=238 days; P=0.003). In the HeartMate II BTT trial, adverse events were similar with the exception of hemorrhagic stroke (M=0.01 versus W=0.04 events per patient years; P=0.02) that occurred more frequently and device related infection (M=0.44 versus W=0.23; P=0.006) that occurred less frequently in women. These results are also supported by a single-center study, wherein sex-specific BTT survival was no different at 1, 6, 12, and 24 months after implantation.

In the ADVANCE HVAD BTT trial, as well as the Continued Access Protocol, after adjustment for baseline differences, there was no sex difference in survival at baseline, 180 days, or 1 year. Women enrolled had a smaller BSA (1.8±0.2 versus 2.1±0.3; P<0.0001) area, less hypertension, and less ischemic cause. At baseline, they were also more likely to have right ventricular failure (increased creatinine and bilirubin), systolic HF, diastolic HF, mean arterial pressure, and pulmonary artery pressure. After implantation, women had similar rates of most adverse events (including hemorrhagic stroke); however, they had increased risk of renal dysfunction and right HF, and they were in need of a right VAD. In this trial, women had more intensive care unit days and a longer total hospital length of stay.

INTERMACS data demonstrates no sex differences in mortality for pulsatile (P=0.82) or continuous flow (P=0.95) devices. Compared with men, women were younger, less likely to be married and had a lower BSA (1.91 versus 2.14; P<0.0001). Interestingly, women tended to be implanted when they were more severely ill, later in the course of their disease.

**Quality of Life Improvements After Transplantation and MCS**

Women experience gains in health-related quality of life (HRQOL) after surgery for advanced HF. In the first year after left ventricular assist device implantation, improvement in HRQOL is seen in both women and men. Women are known, however, to experience more problems with usual activities, anxiety, depression, and pain than men early after implantation. These observations are also seen within the first year after heart transplantation, wherein both groups experience gains in HRQOL; but again, women have more physical functional disability, anxiety, and depression than men. Differences in HRQOL persist >1 year after transplantation. Differences in long-term HRQOL after MCS are not known.
There are also differences in the perception of support by men and women, which may influence HRQOL and other outcomes. There is much to learn about differences in support, as perceived by men versus women, who undergo left ventricular assist device implantation. Findings from the transplant literature may be informative. More satisfaction with social support is related to better HRQOL after heart transplantation, and men have reported more satisfaction with long-term social support after transplantation than women. In addition, in a recent European study, support by women of their male spouses who underwent organ transplantation was related to intent to adhere to medication, but the reverse was not true.

These findings may have relevance for women who undergo MCS implantation. There is a clear need to better understand perception of support by women who undergo MCS implantation, as women more typically provide support to their chronically ill male spouses, rather than receive support.

**Patient Selection and Acceptance**

Thus, women are a minority of recipients of VADs and heart transplants, despite findings that they too experience improved outcomes, including survival and HRQOL. To assess the possibility of sex disparities in the heart transplant selection process, Aaronson et al reported the results of the evaluations of 386 patients being considered for heart transplantation. In spite of being similar to men in regard to age, New York Heart Association Class, duration of HF, left ventricular ejection fraction, cardiac index, higher pulmonary artery wedge pressure, and lower peak oxygen consumption, women were less likely to be listed for transplantation. Women were more likely to be nonwhite, have nonischemic cardiomyopathy, and have a history of substance abuse. Remarkably, the primary reason why women were not deemed acceptable candidates was because of patient refusal. Why do women take themselves out of the game? What factors lead to their choosing optimal medical therapy compared with advanced surgical therapy? Women were more likely to be in the lowest quartile for income (38% versus 22% in men; P=0.01), and lower income was independently associated with nonacceptance for transplantation.

**Conclusions**

The patient described was admitted to the hospital and evaluated for a VAD. She elected to undergo VAD implantation and lived for an additional 4.5 years. It is clear that women are equally as likely as men to have HF; but they are more likely to die from it. Furthermore, they are equally likely to benefit from advanced therapies, including heart transplant and left ventricular assist device. Despite this, women are less likely to be referred for these therapies and if referred, receive them at a later stage. Although the number of heart transplants in women has increased over the past 25 years, only a quarter of recipients are women. Technological advances in MCS that have allowed for patients with smaller BSA to be eligible for implantation have not changed the percentage of women receiving VADs.

It is imperative that we seek to understand these sex differences in delivery of advanced HF therapy. Although current data may suggest under-referral and rejection of therapy by women, factors, such as misperception about body size limitations and body image, may also influence the decision to implant a VAD. Speculation, however, is inadequate to draw conclusions. What is needed are inclusive, adequately powered trials, examining existing data, and using anecdote as a springboard for scientific investigation. Looking toward the future, it is anticipated that the HF prevalence and, therefore, the rate of mortality will continue to rise.

Disclosures

Dr Cook is an advisory board member of Abiomed. Dr Joseph reports minor speaking honoraria from Thoratec and she is an advisory board member of HeartWare. The other authors report no conflicts.

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