Sex differences: implications for heart failure care

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There is a strong interest in differences in the care and outcomes between men and women with cardiovascular disease. In the United States, for example, the Institute of Medicine and Agency for Healthcare Research and Quality have specifically emphasized the need to address disparities in care in order to optimize population health.1 Heart failure has been identified as an important condition in which to evaluate sex differences because of high prevalence, significant morbidity and mortality, and because women constitute the majority of patients with heart failure.2

To date, however, research on sex differences in heart failure has had a limited impact on practice. Inconsistent findings in the literature have left clinicians confused about the implications for clinical care. A majority of previous studies have found that men with heart failure have worse survival than women, but other studies have been neutral and at least one study suggested that women are at higher risk.3–5 At the same time, most studies have suggested that women receive fewer guideline-indicated heart failure therapies, but studies are again mixed.5,6 The inconsistency of study results has been attributed, at least in part, to methodological limitations including non-representative populations, inadequate clinical data for risk adjustment, and limited follow-up. Ultimately, it is difficult to draw firm conclusions from the literature about the magnitude and direction of the problem. In other words, are sex differences real, and if so, are men or women at increased risk?

In this issue, Gustafsson et al. present the results of an ambitious cohort study of 5491 heart failure patients, representing consecutive discharges from 34 Danish hospitals.7 Of note, 40% of the cohort was female, all patients had baseline echocardiography interpreted in a ‘core’ lab, and patients were followed for vital status for 5–8 years after index hospitalization. Therefore, this study addresses several important limitations of previous studies with respect to the representativeness of the study population, the extent of available clinical data, and the length of follow-up.

The primary result of the study was that male sex conferred a 25% increased risk of death over the follow-up period, after adjustment for age and other clinical factors. On the other hand, women were less likely to be treated with ACE inhibitors during hospitalization, even when left ventricular systolic dysfunction was present. An important caveat is that the difference in ACE inhibitor use was more pronounced in elderly patients, especially those over 80 years.

A few limitations of this study should be considered. First, only in-hospital heart failure therapy at the time of the index admission was assessed. Second, there was no ascertainment of the appropriateness of medical therapy in individual cases (i.e. removing patients with contraindications from the denominator of medication use rates), which limits the ability to judge the importance of differences in treatment. Finally, the study enrolment period (1993–1996) precludes assessment of treatment differences and survival in the context of contemporary heart failure care. Nonetheless, the study makes an important contribution to the evidence base for the presence and magnitude of sex differences in heart failure care and outcomes.

The study by Gustafsson et al. also serves as a good example of the challenges of translating evidence of sex differences into clinical action. While men were at increased risk for worse survival, women were less often treated with ACE inhibitors. These seemingly contrary results highlight the importance of a greater understanding of underlying mechanisms for sex differences before clinical care can be altered to address them. It is essential to understand the degree to which observed differences are due to disparities in care delivery, intrinsic biological differences between men and women, and/or unmeasured clinical variation (Table 1).
This leads to a critical question: is it clear that equity in heart failure care should be the goal, or should we promote differential care in order to maximize patient outcomes? If observed sex differences are due to biases in care delivery, then all efforts must be made to promote equitable care. This may be accomplished through increased clinician awareness of disparities and interventions specifically designed to improve care quality for women. To this end, further research is needed to better define the quality gap between men and women—studies in representative heart failure populations that assess treatment in ‘ideal’ candidates for contemporary guideline-based therapies. Heart failure registries may be particularly valuable in quantifying disparities in care and targeting interventions to promote equity because of their ability to reflect evolving heart failure practice. To fulfill this promise, however, registries must have robust clinical data and incorporate longitudinal follow-up of patient care and outcomes.

It is unlikely that observed sex differences will be eliminated by addressing sex biases in care delivery. There is emerging evidence that heart failure care may need to be tailored by sex. First, recent studies reporting higher mortality in women treated with digoxin and less benefit from ACE-inhibitors in women raise the possibility of meaningful sex differences in the response to heart failure therapies.8,9 Second, evidence such as differential adaptation to left ventricular pressure overload and differences in the incidence of ischaemic heart disease and between men and women suggest intrinsic biologic differences in disease manifestation and natural history.2,10,11 Finally, at least some of the sex differences reported in the literature may be due to confounding, with sex reflecting unmeasured clinical risk differences. For example, men with heart failure are more likely to have underlying coronary artery disease, raising the possibility of untreated ischaemia as a mechanism for worse long-term survival. Whether sex differences are the result of differential response to therapy, underlying biologic differences, or unmeasured confounding, ‘one-size-fits-all’ heart failure care may not be appropriate.

Further research is needed to define basic mechanisms of biological differences in disease manifestation and response to therapy between men and women. Studies and registries with detailed clinical risk assessment to account for all potentially important confounders are also warranted. Finally, studies focused on the efficacy of heart failure therapies in women are important, because women have been significantly under-represented in major heart failure clinical trials to date.12,13 This would ideally involve clinical trials with adequate numbers of women to ensure statistical power, but also supplemented by ‘effectiveness’ data from registries and observational studies.

It is certainly possible that all three mechanisms—disparities in the quality of care, unmeasured clinical variation, and underlying biologic differences—play a role in sex differences in heart failure. But until the mechanisms of observed differences are established, separate standards of care for men and women are not appropriate. At this point, the best available evidence indicates that we should strive for equity in care, applying current guidelines for heart failure care to both sexes. In the future, however, the combination of quality improvement initiatives targeting sex disparities and tailored heart failure care by sex may evolve as the best way to optimize outcomes for both men and women.

References

