

Impact of sex and diabetes in patients with heart failure with mildly reduced ejection fraction

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With increasing global awareness of sex differences in the heart failure population and the new entity of heart failure with mildly reduced ejection fraction (HFmrEF), much has yet to be fully understood with regard to patient demographic, clinical presentation, response to guideline-directed heart failure therapies, and outcome across the spectrum of left ventricular ejection fraction (LVEF). A recent study from the UK found that HFmrEF constituted 15% of the entire spectrum of heart failure population, and 40% among this group had LVEF below 50%. The clinical characteristics and outcomes in HFmrEF population were found in a large part to be intermediate between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).¹ These findings were consistent with a previous analysis from European Society of Cardiology (ESC) heart failure long-term registry² as well as a prospective international multiethnic cohort study.³ However, whether HFmrEF is a distinct entity from HFrEF and HFpEF remains a heated debate. On the therapeutic side, whether HFmrEF population demonstrates similar treatment response to guideline-directed heart failure therapies as HFrEF cohorts, requires further evidence from collaborative research efforts. Undoubtedly, the introduction of the HFmrEF entity by the ESC aimed to draw a conjoint effort in better characterisation and to establish a clear therapeutic strategy to this category.

Sex differences in heart failure population was another hot topic in the past decade. While male sex predominated in HFrEF and female sex predominated in HFpEF as shown in various studies, sex differences were also noted with respect to clinical characteristics, pathophysiology and therapeutic responses to heart failure treatment.⁴ Increasing evidence showed that men were predisposed to macrovascular diseases and hence at higher risk of developing HFrEF, whereas women were predisposed to microvascular disease and endothelial inflammation, which were hypothesised to play a key role in HFpEF.⁵ Apart from sex differences in the pathophysiology of heart failure, a number of sex-specific risk factors for heart failure such as

peripartum cardiomyopathy and cancer therapy-induced cardiomyopathy also contributed to distinct sex differences in heart failure populations.

On the other hand, the presence of diabetes was known to be strongly associated with adverse outcomes in both acute and chronic ambulatory heart failure cohorts.^{6,7} Diabetes constitutes an ever-increasing threat to global health as a debilitating and serious chronic disease that causes disabling and life-threatening complications. According to the International Diabetes Federation Diabetes Atlas⁸ published in 2021, some 537 million adults (1 in 10) were living with diabetes in 2021, and the number is expected to rise to 643 million by 2030 and 783 million by 2045. Such an exponential rise in predicted numbers is also anticipated in the Southeast Asia population where 1 in 11 adults (90 million) were living with diabetes in 2021. The under-awareness of diabetes and its profound health consequences continues to be a major challenge to the global healthcare system.

In this issue of the *Annals*, we get an insight into the interplay between these 2 major factors—diabetic status and sex—in the outcome of HFmrEF patients.⁹ The Asian context of this study further adds to the emerging data and understanding of our ethnic population. A systematic collection of data in a nationwide registry is crucial to improving both our understanding as well as clinical care of our heart failure patients. Regarding the clinical characteristics of Asian HFmrEF population shown in the current article, a slight male predominance was observed.⁹ However, the sex predilection was not as clear as in HFrEF or HFpEF cohorts, which had been previously discussed. Obesity was noted to be more prevalent in the diabetic compared with non-diabetic group, and a clear sex predilection was not observed. There was a higher prevalence of prior coronary artery diseases and myocardial infarction in men than women, which was similar to HFrEF cohorts. A higher prevalence of diabetes was observed in women than in men. More importantly, a clear interaction between diabetic status and sex on the outcomes of HFmrEF was demonstrated in this study. Regardless of sex, the presence of diabetes was significantly associated with

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worse clinical outcomes in HFmrEF. However, compared to men, the presence of diabetes in women was found to be less strongly associated with all-cause mortality but more strongly associated with combined cardiovascular death and heart failure rehospitalisation.

While the most widely used classification of heart failure is currently based on the LVEF range and the heart failure treatments that we offer primarily target the physiological consequences of heart failure, little is known on how we can best categorise our heart failure patients. If we are to classify them by ejection fraction, what cutoffs should we use? What is the range that should be considered “normal”? And should we classify “normal” by the response to heart failure therapies in drug trials? Given that the most accepted “reduced ejection fraction group” came mainly from the substantial evidence of drug efficacies in major trials conducted in the past, the HFmrEF group in fact created a lot of enthusiasm and interest in how we can further refine our classification of general heart failure population to optimise the use of heart failure therapies, and perhaps open up a new era of heart failure treatments.

As we understand more about the interaction between sex and various risk factors in heart failure population, as in diabetes in this case, we are expecting to see more research on this topic. With accumulating evidence showing that women behave differently than men in disease processes, outcomes and treatment responses—not only in heart failure but also in other acute and chronic medical illnesses—sex-specific management strategies and guidelines will be one of the important future developments in medicine.

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