EDITORIAL

The fraction we know: heart failure phenotypes and their clinical outcomes

Suraya Kamsani, Prashanthan Sanders

Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia

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Heart failure (HF) affects over 64 million individuals worldwide, and its prevalence is anticipated to rise due to the aging population, increased cardiovascular risk factors, and improved survival rates following HF diagnosis.[1] Since Richard Lower's initial description of HF in 1933, there has been a deliberate endeavor to establish a precise definition for this complex clinical syndrome. This pursuit aims, among others, at fostering consistency in our understanding of the pathogenesis, diagnostic approaches, and management of HF. The first introduction of a distinct HF classification based on ejection fraction (EF) in 2016 by the European Society of Cardiology has accelerated efforts to discern similarities and differences among 3 clinical phenotypes: HF with reduced EF (HFrEF), HF with mid range EF (HFmrEF), and HF with preserved EF (HFpEF).

However, previous pivotal randomized trials conducted between 1980s and early 2000s, focused on what we now recognize as HFrEF, with some overlap with HFmrEF.[2] Interestingly, diagnosing HF as a clinical syndrome rather than relying on strict echocardiographic information in large longitudinal studies, such as the Framingham Heart Study,[3] enables recognition of HF in the absence of impaired systolic heart function, years after the beginning of the study. Similarly, the observational study by Rywik et al,[4] published in this issue of *Polish Archives of Internal Medicine*, covers the intriguing period before and after the contemporary HF classification change. The authors conducted a retrospective analysis of an electronic database encompassing 2601 patients hospitalized in a single tertiary cardiac center between 2014 and 2019. The study aimed to describe the characteristics, survival rates, and prognostic predictors of each HF clinical phenotype, with a majority of patients (61.8%) belonging to the HFrEF, 12.7% to the HFmrEF, and 25.5% to the HFpEF subgroup.

The authors have to be commended for leading the effort to help the readers understand the outcomes of different HF phenotypes in Poland. Within a relatively brief median follow-up of 2.43 years (interquartile range, 1.56–3.49), it was evident that the patients with HFrEF demonstrated the highest mortality rate at 40.5%, in contrast with the HFmrEF and HFpEF phenotypes. This finding aligns with other contemporary population studies.[5,6] Shared prognostic predictors were identified across different HF phenotypes. Notably, utilization of inotropes was consistently associated with an elevated risk of death across all 3 groups, underscoring the advanced stage of the disease. Conversely, the use of angiotensin-converting enzyme inhibitors (ACEIs), known for their cardioprotective effects primarily in HFrEF,[2] independently led to improved clinical outcomes. This finding is particularly intriguing, as randomized trials have failed to show benefits of using ACEIs in the HFpEF phenotype.[7,8] This has baffled many, as hypertension is one of the main drivers of HFpEF and, by logical extension, ACEIs were expected to be highly beneficial. The use of angiotensin receptor blocker, however, was not documented in the study. Another unexpected finding is the potential prognostic benefit of β-blockers in both HFrEF and HFpEF, as again, the published studies have not shown their consistent benefits in the HFpEF phenotype.[9]

It should be noted that a diagnosis of HFmrEF and HFpEF may have been overlooked, not only due to reliance on administrative data and retrospective nature of the study, but also partly due to the absence of a well-established HF phenotyping classification before 2016. The lack of classification could have contributed to a smaller representation of these patients in the study. The inclusion of both emergency and elective hospitalizations added another confounding factor to the heterogeneity of the studied population. Previous research has demonstrated varying outcomes in patients with acute decompensated HF and those with stable HF, with 1-year survival rates ranging from 50% to 60% in acute HF, and

Correspondence to:
Prashanthan Sanders, MBBS, PhD, Centre for Heart Rhythm Disorders, Royal Adelaide Hospital, 1 Port Road, Adelaide, SA 5000, Australia, phone: +61 883139000, email: prash.sanders@adelaide.edu.au
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80% to 90% in stable HF.[5,10,11] Accounting for the nature of the hospital admission (emergency vs elective) as another variable could have provided deeper insights into the study's outcomes. Incorporation of biochemical markers, such as troponin T and N-terminal pro–B-type natriuretic peptide could also further refine the prognostic predictors for each HF phenotype.

Furthermore, beyond the scope of this paper, outcomes may diverge with the implementation of newer guideline-directed medical therapies, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and angiotensin receptor / neprilysin inhibitor. There is still paucity of data on their usefulness in HFpEF, apart from emerging evidence for SGLT-2is.[12]

From an electrophysiologist perspective, we found the use of implantable cardioverter defibrillator (ICD) / cardiac resynchronization therapy-defibrillator (CRTD) most interesting. Although this study showed that ventricular arrhythmia is an important univariate predictor of all-cause mortality in HFrEF, only 56.5% of this subgroup of patients received an implant, thus potentially contributing to a negative association between ICD/CRTD use and prognosis. The lack of data on clinical status, that is, New York Heart Association class, made it difficult to justify the suboptimal rate of a defibrillator implant. Second, ablation provided protective effects in the HFpEF subgroup. As previously described in other studies, atrial fibrillation (AF) is highly prevalent in HFpEF patients.[13] In the discussed study, 64.5% of the HFpEF subgroup had AF, but only 7.6% underwent ablation, and details of the procedure were missing, thus failing to provide meaningful interpretation.

In summary, the study by Rywik et al[4] has provided important insights into stratification of distinct HF phenotypes. However, the evolving landscape of HF leaves many questions unanswered. The proposal of a universal definition and classification of HF set out in 2021 by major international scientific organizations has therefore been enthusiastically received.[14] This long overdue consensus meant that moving forward, provided with a common denominator, we could perhaps gain better understanding of intricate HF syndromes and develop a more comprehensive clinical approach instead of relying on the fraction of knowledge we now possess.

ARTICLE INFORMATION

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CONFLICT OF INTEREST Prashanthan Sanders reports having served on the advisory board of Medtronic, Abbott, Boston Scientific, Pacemate, and CathRx; the University of Adelaide has received on his behalf lecture and/or consulting fees from Medtronic, Abbott, and Boston Scientific; and the University of Adelaide has received on his behalf research funding from Medtronic, Abbott, Boston Scientific, and Becton Dickinson.

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