Time To Rename The Middle Child Of Heart Failure:

Heart Failure With Mildly Reduced Ejection Fraction

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The “middle child” of heart failure (patients with left ventricular ejection fraction [EF] in the 40-50% range) was christened heart failure with mid-range EF in 2014,[1] in recognition of the large gap in treatment evidence in this neglected subgroup of heart failure, with prior clinical trial evidence limited to those patients with EF of 40% or lower, and recent attention being showered upon those with EF of 50% or greater. While the EF 40-50% group was recognized as a “grey area” in prior European Society of Cardiology Heart Failure Guidelines,[2] the name “heart failure with mid-range EF” and acronym “HFmrEF” was adopted in the 2016 guidelines,[3] with the intention of bringing attention to this group of patients and addressing the evidence gap. The adoption of this nomenclature has inspired hundreds of publications which show that HFmrEF constitutes almost a fifth of the heart failure population, with patient demographics intermediate between those with lower and higher EFs, high frequency of coronary artery disease, and better prognosis than those with lower EF.[4]

Importantly, the naming of HFmrEF also prompted a relook at prior randomized controlled trials in heart failure over a broad range of EFs, suggesting that patients with ejection fraction in the lower portion of the HFpEF range, including those who would fall into the HFmrEF (EF 40-50%) category, may benefit from mineralocorticoid antagonists,[5] angiotensin receptor blockers,[6] beta-blockers[7] and digoxin;[8] similar to patients with EF<40% and distinct from patients with higher EF. More recently in the largest outcomes trial of heart failure with EF≥45% to date, the PARAGON-HF trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in Heart Failure and Preserved Left Ventricular

Ejection Fraction),[9] a significant EF-by-treatment interaction was observed, whereby sacubitril/valsartan, compared with valsartan, reduced the likelihood of the primary composite outcome of cardiovascular death and total heart failure hospitalizations by 22% in those with EF below the median of 57% (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.64–0.95), but with essentially no effect on the composite primary outcome in those with EF>57% (HR 1.00; 95% CI 0.81–1.23). Taken in the context of robust trial evidence of the benefit of neurohormonal agents in heart failure with EF<35-40%, including sacubitril/valsartan in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, these data suggest that prior trials may have used too low a cutoff of EF to define "reduced" EF (a cutoff that was itself arbitrarily chosen to enrich for events), and that patients with EF lower than normal, who probably benefit from such therapies, may in fact be more appropriately renamed as "heart failure with mildly reduced EF".

Beyond nomenclature, the recent trial evidence also call to question the cutoffs with which we define "mildly reduced" EF. As a continuous variable with a normal distribution within the population, the threshold value to define "normal" versus "reduced" EF is arbitrary. Guidelines from the American Society of Echocardiography and European Society of Echocardiography define a normal EF as >55%. Indeed, Framingham Heart Study participants with EF 50-55% were at greater risk of HF and death compared to those with EF>55%.[7] Notably, the "normal" distribution of EF rises with age and is higher in women than men in the general population,[10] since EF is a fraction which increases as the heart remodels and left ventricular end-diastolic volume

(denominator) shrinks out of proportion to the stroke volume (numerator). Using a common EF cutoff of, say, 50% to define "normal" would therefore include elderly women who actually have relatively reduced EF for their age and sex. Such sex differences may explain the observation in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, where women appeared to benefit across the EF spectrum beyond 55%, but men only at EF lower than ~55%.[5] Further supporting this concept, in combined PARAGON-HF and PARADIGM-HF data,[11] treatment effect splines across the entire EF spectrum showed efficacy of sacubitril/valsartan in the EF 40-50% range, with the upper 95% confidence interval boundary of the rate ratio for sacubitril/valsartan versus comparator renin-angiotensin blockade remaining below 1.0 (indicating benefit with sacubitril/valsartan) up to EF ~55%, and sex-specific splines indicating that the benefit of sacubitril/valsartan persisted to higher EFs in women compared to men.[12] While such approaches may provide clinically meaningful evidence for an EF cutoff selection that was previously based on available trial evidence,[13] we acknowledge that these post-hoc analyses should be regarded as hypothesis-generating only. We further acknowledge the potential for age- and ethnicity- specific EF cutoffs in addition to sex; yet heart failure is largely a disease of the elderly and robust evidence for ethnic heterogeneity of treatment response in heart failure is lacking.

Pertinent to any discussion on EF cutoffs are the considerations that (i) the methods by which we measure EF are known to be imprecise, and (ii) EF measurements can change over time in the same patient.[13, 14] The reliability of EF determination by

echocardiography —the technique most commonly used clinically— showed an interobserver variability of 8% to 21% and an intraobserver variability of 6% to 13%.[15] Furthermore, while there were minor differences in EF measured by echocardiography compared to cardiac magnetic resonance imaging, left ventricular volumes by echocardiography were smaller and more variable than those obtained by cardiac magnetic resonance imaging.[16] Added to this, EF has been shown to change over time in patients with heart failure, with more than a third of patients crossing the EF 50% threshold in either direction during longitudinal surveillance.[17] Thus, the strict application of cutoffs to individual patients has a high potential for mis-classification. Given these considerations, is it meaningful in the first place to classify patients using EF? Such discussions have been raised time and again, reminiscent of the discussion of blood pressure cutoffs with which to define hypertension; and calls have been made to shift to etiology-based classification of heart failure instead of EF. Yet at the end of the day, EF remains a cornerstone of all current heart failure guidelines and the most clinically useful criterion to guide treatment decisions in clinical practice, since clinical trials that form the basis of evidence-based treatment recommendations are all predicated on EF cutoffs.

If classification of heart failure by EF is here to stay (at least for the near future), how may we use more recent insights to better inform our classification using EF?[18] A simplification to two instead of three categories, by lumping HFmrEF under "reduced" EF (using a cutoff of, say, <50%), would appear most straightforward and easy to implement.[19] Indeed, the Australian 2018 heart failure guidelines came to this conclusion.[20] However, grouping patients with "mildly reduced" and more severely

reduced EF under the same umbrella would fail to recognize the different magnitudes of treatment effect and their strengths of evidence, as well as the different prognosis and risk-benefit ratios, in HFmrEF versus those with lower EFs. On the other hand, grouping patients with EF below 50% (or 55%) under the common term "reduced", while still distinguishing between those with "mildly reduced" versus more severely reduced EF, would acknowledge the smaller relative and absolute benefits, as well as the lower strength of evidence, of neurohormonal antagonists in HFmrEF compared to heart failure with EF<40%. Of note, the Australian 2018 heart failure guidelines[20] gave different strength of recommendations and quality of evidence for heart failure with a moderately/ severely reduced EF (<40%) (Strong recommendation/ High quality of evidence) compared to heart failure with mildly reduced EF (41-49%) (Weak recommendation/ Low or very low quality of evidence) for various neurohormonal therapies.

Thus, a renaming of HFmrEF as "heart failure with mildly reduced EF" might solve some of these issues of nomenclature. While it is tempting to prescribe specific EF cutoffs, we recognize that there will be debate about what constitutes "mildly reduced", what these cutoffs should be, and whether they should be different for men and women. Nevertheless, the new nomenclature would send an important signal to clinicians to consider treating these patients with neurohormonal agents known to be beneficial in patients with heart failure and more severely reduced EF, thus enlarging the treatment population and reducing the risk that patients with mildly reduced EF, especially women, who are deprived of potentially beneficial therapies. Such reclassification would accordingly shrink the population of heart failure with higher EFs for which we still have

no evidence of treatment outcome benefits – a group perhaps aptly named “heart failure with normal EF (≥50 or 55% in men and ≥55 or 60% in women)” although precise cutoffs remain controversial since “normal” EF may also vary with factors other than sex (such as age and ethnicity). Furthermore, the presence of a very high EF should prompt a search for pathology, such as cardiac amyloidosis or hypertrophic cardiomyopathy, where shrinkage of the left ventricular end-diastolic volume (denominator of EF) leads to “supra-normal” EF.[21] Any revised nomenclature would impact estimates of prevalence and incidence of the different forms of heart failure, carrying implications for resource utilization that healthcare providers, regulators and payers will need to grapple with.

Given the totality of the evidence, we propose renaming "heart failure with mid-range ejection fraction" as “heart failure with mildly reduced ejection fraction” and considering sex-based cutoffs in the definition. The implications of this new nomenclature are three-fold: (i) attempts should be made to obtain as precise a measurement of EF as possible in patients with heart failure, especially in those whose EF measurements are borderline, to avoid misclassification; (2) patients with a mildly reduced EF should be given the benefit of the doubt and considered for treatment with established therapies in HF with more severely reduced EF; (3) future clinical trials for heart failure with reduced EF may consider enrolling patients with EF up to the normal range.

Disclosures: C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has

served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder & non-executive director of eKo.ai.

A.A.V. received consultancy fees and/or research grants from: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myokardia, Novartis, NovoNordisk, Roche Diagnostics.

J.J.V.M: Consulting payments to Glasgow University: Bayer, Cardiorentis, Amgen, Theracos, Abbvie, DalCor, Pfizer, Merck, AstraZeneca, Glaxo Smith Kline, Bristol Myers Squibb, Vifor-Fresenius, KRUK, Novartis, Cardurion, Alnylam Pharmaceuticals, Cyclerion. All payments were made through a consultancy with Glasgow University and were not personal payments.

S.D.S. has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya.

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