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EDITORIAL COMMENT

Cardiac Ejection Fraction

New Insights About its Dynamic Nature*

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Heart failure (HF) is the fastest growing form of cardiovascular disease (1-3), and guidelines for its management have been developed in both the United States and Europe (2-4). Ejection fraction (EF) is arguably the most important and influential factor in HF because it is the basis for dichotomizing all patients with HF into the current classification of either preserved EF (HFpEF) or reduced EF (HFrEF) forms of the disease (2-4), thereby significantly influencing patients' management, including drug selection. It is also perhaps the most common parameter used by clinicians for assessing risk factors and prognosis in an individual patient (5), although EF may not correlate with the degree of functional limitations in many patients.

EF is second only to New York Heart Association functional class in criteria used for patient selection in HF trials (6), and it is a common secondary endpoint to demonstrate potential benefit in nearly all clinical trials to evaluate new therapeutic interventions for patients with HF and reduced systolic function (7). However, aside from beta-blockers (8), the change in EF with current HF guideline drugs has been small and not commensurate with the significant reduction in mortality observed (2-4). This observation emphasizes the importance of altering pathophysiology over change in contractile function because most pharmacological agents that have a direct inotropic effect have been associated with increased mortality, largely related to sudden death when these agents are used for chronic HF (9). These observations have raised the question whether structural and functional changes have rendered EF as a trial endpoint somewhat obsolete (10). There are a number of new endpoints being examined in clinical HF trials (11), with increasing emphasis on the use of biomarkers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) (12).

Despite the importance of EF in the management of patients with HF, the dynamic nature of EF over time is perhaps underappreciated. Several large observational studies have examined the change in EF over time (13-15), including the IMPROVE HF registry (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) (13), which showed that >1 in 4 subjects had >10% increase in EF by 2 years of follow-up. The largest previously reported observational study of the natural history of EF was from a community-based cohort of 2,413 patients enrolled after an HF hospitalization for either reduced (n = 800) or preserved (n = 1,613) EF (15) and followed up for an average of 4.1 years (range: 0.8 to 8.8 years), with no attempt to standardize oral HF therapy. These investigators documented a total of 8,163 transitions between HFrEF and HFpEF or death during the follow-up period, with equal percentages of patients who transitioned from HFpEF to HFrEF (22%) or from HFrEF to HFpEF (23%).

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In this issue of the *Journal,* Lupón et al. (16) report on an important prospective observational registry designed to examine the trajectory of the EF in a consecutive series of 1,160 patients with an initial EF <50% who were enrolled over a 15-year period from August 2001 to December 2015. It was a homogeneous group of patients because all subjects lived in a region near Barcelona, Spain and included mostly men (76.5%), with an average age of 64.9 years and with the majority (57.1%) having HF of ischemic origin. Although 70.4% of the study patients were considered to be in New York Heart Association

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functional class II at study entry, the average EF was 30.4 ± 7.4%, the median NT-proBNP was 1,623 (range: 709 to 3,709), and the overall mortality rate was 72% at 15 years. The study patients had a combination of the comorbidities, such as hypertension, diabetes, and renal insufficiency (16), seen in most patients with HF. All subjects had a transthoracic echocardiogram obtained at baseline and 1 year and were then scheduled for follow-up every 2 years to measure EF. There was a total of 4,183 echocardiograms performed, with an average number of studies of 3.6 ± 1.7 per subject. These studies were all read by dedicated echocardiography faculty to minimize inter-reader and intrareader variability.

This consecutive series (16) has the longest follow-up for examining changes in EF ever reported, and what separates this study from all previous trials is that the treating physicians were all HF cardiologists from a single university practice who committed to adhere to the published guidelines of international societies for HF management (2–4) throughout the 15-year period of the study, regardless of changes in EF. This protocol provided the best observation of the natural history of EF changes in patients receiving the best therapy available.

One of the most important observations from the study was the inverted-U shape of change in EF over time, with a steep rise phase of greatest improvement noted during the first year of enrollment, particularly in patients with new onset (<1 year) HF, then a decade of a plateau phase with little change in EF, followed by a slow decline phase over time in most patients. It is unclear from the data what percentage of patients had newly diagnosed HF and were naïve to oral HF therapy, but baseline medications reflect fairly complete HF regimens. Overall, 56% of subjects with HFrEF had no change in EF category over time, whereas 21% moved up to the HF with moderately reduced EF (HFmrEF) group (EF 40% to 48%), and 23% fully recovered to an EF >50%. This finding emphasizes the importance of adhering to guidelines, including target dosing (9).

Collectively, the study by Lupón et al. (16) and the other longitudinal studies on EF teach us the following about potential changes in EF over time (13–16): changes in EF over time are not uniform, and there may be equal percentages of improvement and decline; women typically have a higher EF at baseline than men and are more likely to improve with initial treatment, but their EF decline may be equivalent to that of men in the long term; a nonischemic cause of HF is associated with the greatest increase in EF in year 1 (9 ± 12%), especially if HF is secondary to hypertension, and these patients experience less of a decline over time; patients with a shorter duration of symptoms of HF are more likely to experience the greatest recovery of function; beta-blockers (vs. all other HF medications) are associated with the greatest and most sustained improvement in EF.

The other important lesson from this study is the increased mortality in patients who exhibited a decline in EF between scheduled echocardiograms while receiving appropriate HF therapy, with the degree of risk directly related to the absolute decline in EF from the last measurement. This finding occurred more in men with HF of ischemic origin, but it also occurred in women over time. A decline in EF should alert clinicians who are following patients with HF to increase the frequency of follow-up visits for these patients and to consider referral to an HF center for evaluation of more advanced therapies when appropriate. It also raises the question of the optimal frequency of determining EF over time to identify patients who may have a significant decline in EF with a modest change or even an absence of worsening symptoms.

The study by Lupón et al. (16) also draws attention to the newly defined phenotypes with reduced EF, including patients with HFmrEF (2). Although patients with HFmrEF had a higher average EF at baseline (44% vs. 30%) than the HFrEF group, they had a smaller increase in EF during year 1 (3% vs. 9%), with an EF that remained higher for up to 9 years, but a lower EF at study end. There is also growing interest in patients with so-called midrange EF (17), as well as the group with nearly complete or complete recovery of function (18,19). These newly identified subgroups or phenotypes suggest that the current dichotomy of HF into either HFrEF or HFpEF is evolving into a more nuanced taxonomy (20,21), and they reinforce the growing need both for clinicians to focus on specific causes of HF such as hypertension and for the development of new guidelines (22).

The few shortcomings of the study by Lupón et al. (16) include its homogeneous population, largely consisting of men from a specific culture, that may not allow the results to be fully extrapolated to other groups of patients with HF, as well as the lack of documentation of the average doses of the HF drugs, which are important components of HF guidelines (2–4). However, this rich dataset will provide important benchmarks on the variable trajectory of EF even in patients managed according to national HF guidelines over a long period. The impressive improvements documented during year 1 of management in this study suggest that timing of enrollment of patients with HFrEF into HF clinical trials may warrant delay for potentially up to 1 year to realize all the possible

benefits of guideline-directed therapy, especially patients with new onset HF.

The study by Lupón et al. (16) is an important contribution to the field of HF. It provides the best current information on the dynamic nature and changing trajectory of EF over time, with potentially nearly equal transitions to both improvement and decline. The study also confirms that many factors influence the variable trajectory of each cause of HF. These observations provide a strong endorsement for managing all patients with HF according to the evidence-based published guidelines developed by HF societies (2–4) for the management of patients with HFrEF, especially during the first year of treatment and regardless of severity of limitations induced by symptoms or level of reduced EF, and they also emphasize the need to close the gap between guidelines and practice (23). This rich dataset, and subsequent additional analyses from this unique registry, will provide important lessons for clinical management and benchmarks for many future studies in HF.

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REFERENCES

1. Heidenreich PA, Albert NM, Allen LA, et al., American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606–19.

2. Ponikowski P, Voors AA, Anker SD, et al., Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;14:2129–200.

3. Yancy CW, Jessup M, Butler J, et al. 2017 ACC/AHA/HFSA focused update on the 2013 ACC/AHA guidelines for the management of heart failure: ACC/AHA/HFSA Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:776–803.

4. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacologic therapy for heart failure: an update of the 2013 ACC/AHA/HFSA guideline for management of heart failure: a report on the ACC/AHA Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1476–88.

5. Echouffo-Tcheugui JB, Erqou S, Butler J, Yancy CW, Fonarow GC. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. J Am Coll Cardiol HF 2016;4:237–48.

6. Bjork JB, Alton KK, Georgiopoulou VV, Butler J, Kalogeropoulos AP. Defining advanced heart failure: a systematic review of criteria used in clinical trials. J Card Fail 2016;22:569–77.

7. Bloom MW, Greenberg B, Jaarsma T, et al. Heart failure with reduced ejection fraction. Nat Rev Dis Primers 2017;3:17058.

8. Bristow MR, Gilbert EM, Abraham WT, et al., MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807–16.

9. Toma M, Starling RC. Inotropic therapy for end-stage heart failure patients. Curr Treat Options Cardiovasc Med 2010;12:409–19.

10. Bristow MR, Kao DP, Breathett KK, et al. Structural and functional phenotyping of the failing heart: is the left ventricular ejection fraction obsolete? J Am Coll Cardiol HF 2017;5:772–81.

11. Patel RB, Vaduganathan M, Samman-Tahhan A, et al. Trends in utilization of surrogate endpoints in contemporary cardiovascular clinical trials. Am J Cardiol 2016;117:1845–50.

12. Ibrahim NE, Gaggin HK, Konstam MA, Januzzi JL Jr. Established and emerging roles of biomarkers in heart failure clinical trials. Circ Heart Fail 2016;9:e002528.

13. Wilcox JE, Fonarow GC, Yancy CW, et al. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. Am Heart J 2012;163:49–56.

14. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012;5:720–6.

15. Clarke CC, Grunwald GK, Allen LA, et al. Natural history of left ventricular ejection fraction in patients with heart failure. Circ Cardiovasc Qual Outcomes 2013;6:680–6.

16. Lupón J, Gavidia-Bovadilla G, Ferrer E, et al. Dynamic trajectories of left ventricular ejection fraction in heart failure. J Am Coll Cardiol 2018;72:591–601.

17. Hsu JJ, Ziaeian B, Fonarow GC. Heart failure with mid-range (borderline) ejection fraction: clinical implications and future directions. J Am Coll Cardiol HF 2017;5:763–71.

18. Merlo M, Stolfo D, Anzini M, et al. Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? J Am Heart Assoc 2015;4:e001504.

19. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016;1:510–8.

20. Wilcox JE, Yancy CW. Heart failure: a new phenotype emerges. JAMA Cardiol 2016;1:507–9.

21. Bozkurt B, Colvin M, Cook J, et al., American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. Circulation 2016;134:e579–646.

22. Yancy CW, Fonarow GC. The new hypertension guidelines: compelling population benefit, manageable risk, and time to implement. JAMA Cardiol 2018 May 23 [E-pub ahead of print].

23. Biglane JB, Becnel MF, Ventura HO, Krim SR. Pharmacologic therapy for heart failure with reduced ejection fraction: closing the gap between clinical guidelines and practice. Prog Cardiovasc Dis 2017;60:187–97.

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