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EDITORIAL COMMENT

Left Ventricular Ejection Fraction

What Is "Normal"?*

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As the population in the United States ages, the prevalence of heart failure (HF) continues to increase, with approximately 915,000 new HF cases diagnosed annually and >8 million people in the country projected to have HF by 2030 (1,2). Despite advances in medical and device therapy for HF over the past few decades, mortality from HF remains high, with approximately 50% mortality within 5 years of HF diagnosis (3). Additionally, the total costs of HF in the United States are projected to increase to $70 billion by 2030. Given the poor prognosis and growing financial costs of treating HF, the development of effective methods to prevent HF is crucial, and identifying populations at increased risk for developing HF may be the most efficient way to do so. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines classify these patients have having Class A or B HF; risk factors for developing HF are well-established and include hypertension, diabetes mellitus, metabolic syndrome, and atherosclerotic disease (4). The high prevalence of these conditions, however, begs the question of how we can narrow our focus to target the at risk population.

The current ACCF/AHA guidelines classify patients with a left ventricular ejection fraction (LVEF) of ≥50% as having a preserved ejection fraction (4), and previous studies have found that asymptomatic patients with lower LVEF are at greater risk of developing HF. In a study of patients with untreated hypertension, an LVEF of <50% was associated with a 10-fold increased risk of incident HF, compared with patients with an LVEF of >50% (5). Similarly, in the MESA (Multi-Ethnic Study of Atherosclerosis) study, an LVEF of <50% was associated with a 12-fold increased risk of HF and 3.5-fold increased risk of all-cause mortality (6). Additionally, in the Framingham Heart Study database, even patients with an intermediately reduced LVEF of 40% to 50% were at greater risk of incident HF (hazard ratio, 3.3) and mortality (hazard ratio, 1.6), compared with patients with an LVEF of >50% (7). Taken together, these studies strongly suggest that an LVEF of <50% is associated with the development of HF. However, with the "normal" classification for LVEF being set at 55% to 65% and an increased risk for HF associated with an LVEF of <50%, this raises the question as to whether there is any increased risk among patients that fall in the 50% to 55% range.

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In their study published in this issue of *JACC: Heart Failure*, Tsao et al. (8) make use of the extensive echocardiographic data available in the Framingham Heart Study database to retrospectively evaluate whether community-based, asymptomatic patients with a borderline LVEF, defined in their study as 50% to 55%, developed worse outcomes compared with patients with a preserved ejection fraction (LVEF >55%). Specifically, over a median follow-up period of approximately 8 years, they assessed for the composite outcome of HF or death, as well as the secondary outcome of incident HF. Because this study was performed on a community-based cohort without a previous history of HF, a vast majority of the participants (94.9%) had a normal LVEF of >55%, and

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only 3.5% of the participants included in the study had a borderline LVEF. Using a variety of models, their categorical analyses show that participants with a borderline LVEF had intermediate risks of the composite outcome of HF or death as well as the secondary outcome of incident HF, with higher risks than participants with an LVEF of >55% and lower risks than participants with an LVEF of <50%. Additionally, their continuous analyses reveal a linear inverse relationship between LVEF and these outcomes as well, with a 23% increased risk of HF seen with every 5% decrease in LVEF.

With the long-term follow-up available in the Framingham Heart Study, Tsao et al. (8) use multiple models to provide robust support for their findings. Nevertheless, there are some important limitations of the study, as acknowledged by the authors, including its observational nature, the lack of ethnic heterogeneity of its participants, and the older imaging methods used to assess LVEF. Specifically, the de Simone method was used for most of their study population, and the biplane Simpson's method was used for a smaller subset; nonetheless, their secondary analysis evaluating the 2 methods found good correlation and agreement between them.

This study expands on prior work showing that a mildly depressed LVEF is associated with a higher risk of developing HF and greater mortality (7,9) and is the first to evaluate specifically the long-term outcomes of asymptomatic patients with a "borderline" LVEF of 50% to 55%. These findings raise many intriguing questions, including "What is a 'normal' LVEF?" Guidelines suggest that a normal or preserved LVEF is >50% (4), and as echocardiography reports of patients with an LVEF 50% to 55% commonly denote them as having "low-normal" LVEF, these patients may often be considered to have the same prognosis of patients with an LVEF of >55%. However, the authors show that this group is more likely to develop HF or die. The persistence of increased risk beyond the arbitrary cutoff of 50% is not entirely surprising. Similar to the findings in this study, Yeboah et al. (6) previously showed a continuous inverse association with LVEF and risk of HF and death in the MESA cohort, with every 10% decrement in LVEF associated with approximately a 2-fold increased risk of HF and 22% increased risk of all-cause mortality. Taken together, these findings suggest that an LVEF of 50% to 55% should not be considered within the "normal" range, because patients within this group may be at higher risk of developing HF than the general population.

More studies are needed to reinforce these associations, particularly to a more geographically and ethnically heterogeneous population, and better understand the reasons for the increased risk seen in this group. The use of more advanced imaging modalities for assessing LVEF, such as cardiac magnetic resonance imaging, may provide better resolution to these data. In fact, the study by Yeboah et al. (6) used cardiac magnetic resonance imaging data in their analysis of the MESA cohort, and expanding their findings to the group of patients with LVEF 50% to 55% would be of great interest and could provide strong support for the current study. To better identify high-risk populations, it may be beneficial to incorporate additional risk factors in future studies, particularly renal function, which was not included in this study. Additionally, incorporation of biomarkers into future studies, such as brain natriuretic peptide and high-sensitivity troponin assays, may help to improve the specificity of their findings. The recent STOP-HF (St. Vincent's Screening to Prevent HF) trial showed that brain natriuretic peptide-based screening may help prevent the onset of LV dysfunction and HF (10), and high-sensitivity cardiac troponin T has been associated independently with incident HF in the Atherosclerosis Risk in Communities study (11).

As the identification of high-risk groups becomes further refined, determining how to treat this population to effectively prevent the onset of HF is the next challenge. In light of the results presented by these investigators, asymptomatic patients with a borderline LVEF likely warrant closer follow-up or possibly referral to a cardiologist for further evaluation. Addressing any underlying risk factors, such as hypertension and diabetes, is paramount, yet the optimal way to treat these comorbidities in this setting is still unknown. Neurohormonal blockade (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, aldosterone antagonists) is reasonable, because the development of HF is related to progressive maladaptive signaling of the sympathetic nervous system and renin-angiotensin-aldosterone system. Although these agents have thus far been shown to not be effective in improving cardiovascular outcomes in patients with existing HF with preserved ejection fraction, whether their use can help to prevent the onset of HF requires further evaluation. With regard to the management of diabetes in this population, there has been much attention on the relationships between glucose-lowering medications and HF outcomes. The recently published results of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Event) Trial showed a decrease in HF hospitalization in patients treated with empagliflozin, an inhibitor of

sodium-glucose transporter 2 (12). Nonetheless, further studies are necessary to determine the optimal strategy to prevent the onset of HF in this population.

In summary, the current study encourages physicians to reexamine how patients with "borderline" or "low-normal" LVEF are viewed and managed. As the authors point out, these terms may be misleading, with those with borderline or low-normal LVEF being at increased risk, and perhaps the definition of a "normal" LVEF should be reconsidered. Furthermore, deeper examination of this targeted group of patients may help to pave the way to developing strategies to effectively curb the rising prevalence of HF.

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REFERENCES

1. Heidenreich PA, Albert NM, Allen LA, et al. 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. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133:447–54.

3. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996–1004.

4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

5. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Porcellati C. Asymptomatic left ventricular systolic dysfunction in essential hypertension: prevalence, determinants, and prognostic value. Hypertension 2005;45:412–8.

6. Yeboah J, Rodriguez CJ, Stacey B, et al. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2012;126:2713–9.

7. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977–82.

8. Tsao CW, Lyass A, Larson MG, et al. Prognosis of adults with borderline left ventricular ejection fraction. J Am Coll Cardiol HF 2016;4:502–10.

9. Hobbs FDR, Roalfe AK, Davis RC, Davies MK, Hare R, Midlands Research Practices Consortium (MidReC). Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). Eur Heart J 2007;28:1128–34.

10. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310:66–74.

11. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. J Am Coll Cardiol HF 2014;2:600–7.

12. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™). Cardiovasc Diabetol 2014;13:102.

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