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Prognosis of Adults With Borderline Left Ventricular Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to examine the association of a borderline left ventricular ejection fraction (LVEF) of 50% to 55% with cardiovascular morbidity and mortality in a community-based cohort.

BACKGROUND Guidelines stipulate a LVEF >55% as normal, but the optimal threshold, if any, remains uncertain. The prognosis of a "borderline" LVEF, 50% to 55%, is unknown.

METHODS This study evaluated Framingham Heart Study participants who underwent echocardiography between 1979 and 2008 (n = 10,270 person-observations, mean age 60 years, 57% women). Using pooled data with up to 12 years of follow-up and multivariable Cox regression, we evaluated the associations of borderline LVEF and continuous LVEF with the risk of developing a composite outcome (heart failure [HF] or death; primary outcome) and incident HF (secondary outcome).

RESULTS During follow-up (median 7.9 years), HF developed in 355 participants, and 1,070 died. Among participants with an LVEF of 50% to 55% (prevalence 3.5%), rates of the composite outcome and HF were 0.24 and 0.13 per 10 years of follow-up, respectively, versus 0.16 and 0.05 in participants having a normal LVEF. In multivariable-adjusted analyses, LVEF of 50% to 55% was associated with increased risk of the composite outcome (hazard ratio [HR]: 1.37; 95% confidence interval [CI]: 1.05 to 1.80) and HF (HR: 2.15; 95% CI: 1.41 to 3.28). There was a linear inverse relationship of continuous LVEF with the composite outcome (HR per 5 LVEF% decrement: 1.12; 95% CI: 1.07 to 1.16) and HF (HR per 5 LVEF% decrement: 1.23; 95% CI: 1.15 to 1.32).

CONCLUSIONS Persons with an LVEF of 50% to 55% in the community have greater risk for morbidity and mortality relative to persons with an LVEF >55%. Additional studies are warranted to elucidate the optimal management of these individuals. (J Am Coll Cardiol HF 2016;4:502–10) © 2016 by the American College of Cardiology Foundation.

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Clinical heart failure (HF) is associated with substantial morbidity and mortality, despite advances in medical therapy (1). Characterization of at-risk populations is essential to understand the development of HF and to target potentially susceptible persons for preventive strategies.

European Society of Cardiology and American Society of Echocardiography guidelines report normal left ventricular ejection fraction (LVEF) values as >50% and >55%, respectively (2,3). Clinical trials of HF have defined LVEF <40% to 45% as indicating left ventricular (LV) systolic dysfunction (4,5). However, groups with an asymptomatic LVEF of 40% to 50% show greater risk for HF and mortality compared with groups with an LVEF >50% to 55% (6–8). This finding has led investigators to question the optimal cutpoint for identifying a "normal" LVEF and to ask whether the association of LVEF with adverse cardiovascular outcomes is continuous (9).

SEE PAGE 511

In particular, the prognosis for those persons with a "borderline" LVEF of 50% to 55% is unclear. We hypothesized that these persons are at greater risk for developing cardiovascular events and death relative to persons with an LVEF >55%. Accordingly, we characterized the clinical correlates and prognosis of persons with an LVEF of 50% to 55% and the relationships of continuous LVEF with adverse outcomes in a large community-based cohort.

METHODS

PARTICIPANTS. The details of the selection criteria and examination of Framingham Heart Study (FHS) original and offspring cohorts have been described (10,11). We included original cohort participants who attended examinations 16 (1979 to 1981) or 20 (1988 to 1989) and offspring cohort participants who attended examinations 4 (1987 to 1990), 6 (1995 to 1998), or 8 (2005 to 2008) (Online Figure 1). Of 14,187 eligible person-observations, we excluded observations with a history of HF (n = 270), inadequate echocardiographic data (n = 3,592), and a lack of follow-up data (n = 104). Persons with missing measures were more likely to be obese and to have greater CVD risk factors (12). After exclusions, we included 10,221 person-observations representing 5,334 unique persons. The number of observations included at each examination is presented in Online Table 1.

Diabetes was defined as a fasting glucose concentration ≥126 mg/dl or the use of hypoglycemic medications. Systolic and diastolic blood pressures were measured as the average of 2 measurements made on seated participants by using a mercury column sphygmomanometer, an appropriately sized cuff, and a standardized protocol. Use of antihypertensive medications and antidiabetes medications was self-reported, and all medications were verified by the FHS clinic physician. Between January 1995 and September 1998, plasma brain natriuretic peptide levels were collected in offspring cohort participants (n = 2,552) at examination 6, in the morning after an overnight fast. Samples were stored at −70°C and were analyzed using sensitive noncompetitive immunoradiometric assays (Shionogi, Japan) in June 1999.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CVD = cardiovascular disease
FHS = Framingham Heart Study
HF = heart failure
HFPEF = heart failure with preserved ejection fraction
HFREF = heart failure with reduced ejection fraction
HR = hazard ratio
LVEDD = left ventricular end-diastolic dimension
LV = left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction

ECHOCARDIOGRAPHY AND CALCULATION OF LVEF. The following ultrasound machines were used for echocardiography: for original cohort examination cycles 16 and 20 and for offspring examination cycles 4 and 5, Hewlett Packard model 77020AC (Hewlett Packard, Palo Alto, California); and for offspring examinations 6 and 8, Hewlett Packard Sonos 1000 and Sonos 5500, respectively.

Measurements of M-mode LV end-diastolic dimension (LVEDD) and end-systolic dimension were performed by experienced sonographers using the leading edge technique according to American Society of Echocardiography guidelines (13). LVEF was calculated with these measures using the Z-volume formula by de Simone et al. (14):

$$LVEF\ (\%) = \frac{[(4.5 \cdot LVEDD^2) - (3.72 \cdot LVESD^2)]}{4.5 \cdot LVEDD^2} \cdot 100$$

where *LVESD* is LV end-systolic dimension.

The basis of this method is human (14) and experimental (15) evidence that the epicardial long axis-to-short axis ratio is constant through the cardiac cycle and has been widely applied in clinical studies (16–18). We selected this formula to include the longer follow-up of earlier cohorts that did not have routine 2-dimensional quantitation of chamber volume.

Additionally, in a subset of participants, both the de Simone method and the biplane Simpson method using 2-dimensional echocardiography (available in n = 2,315 of offspring cohort at examination 8) were used to quantitate LVEF by the summation of disks method in 4-chamber and 2-chamber views (3).

FOLLOW-UP. Participants' medical records were reviewed and adjudicated for cardiovascular disease (CVD) and death. CVD included history of coronary artery disease, stable and unstable angina, myocardial