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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).

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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

infarction (MI), cerebrovascular accident (atherothrombotic brain infarct, transient ischemic attack, intracranial or subarachnoid hemorrhage, cerebral embolism), and peripheral arterial disease (intermittent claudication).

The diagnosis of HF was made using the FHS criteria (19), with sensitivity and specificity comparable to other HF criteria (20). The date of onset of HF was noted as the first episode of HF symptoms, physician visit, or hospitalization. HF with a reduced LVEF (HFREF) and HF with a preserved LVEF (HFPEF) were defined as HF symptoms with an LVEF <50% and ≥50%, respectively (21).

Our primary outcome was a composite of new-onset HF and death because death may be the first adverse event in persons with asymptomatic LV systolic dysfunction (6).

STATISTICAL ANALYSIS. We pooled participants of FHS original cohort examinations 16 and 20 and of offspring cohort examination cycles 4, 6, and 8, and we retained participants free of prevalent HF. Participants were grouped by LVEF <50%, 50% to 55%, and >55%, calculated on the basis of their examination echocardiograms. We evaluated clinical correlates of borderline LVEF relative to LVEF >55% (excluding participants with LVEF <50%), by using multivariable logistic regression with the following covariates: age, sex, baseline CVD, diabetes, systolic blood pressure, diastolic blood pressure, and treatment of hypertension.

We followed participants for incident HF or death during a follow-up period of up to 12 years. Ten-year age- and sex-adjusted incidence rates of HF by LVEF category were estimated using the data-augmentation method (22). Cumulative incidence curves describing the occurrence of these outcomes by ejection fraction category were presented. The proportions of participants in whom HFPEF and HFREF developed at follow-up were determined for each LVEF group. The hazard ratio (HR) for these outcomes was compared among the categories of LVEF, with LVEF >55% serving as the referent group. We estimated age- and sex-adjusted and multivariable-adjusted proportional hazards models for each outcome, after confirming that the assumption of proportionality of hazards was satisfied for each outcome. We also examined continuous LVEF as a risk factor for these outcomes. Primary models were stratified by cohort type and presence versus absence of prevalent MI. To address possible confounding from time (as a result of changes in echocardiography quality, CVD risk factor prevalence, and CVD treatment during the study), we examined similar models that stratified by examination and prevalent MI.

We also conducted a secondary analysis examining the association of LVEF calculated by the biplane Simpson method, available in offspring participants at examination 8, with our outcomes of interest. The Pearson correlation coefficient, Bland-Altman method (23), and weighted kappa statistic (24) were used to assess the agreement between LVEF calculated by the de Simone and Simpson biplane methods. Final models were repeated using the robust Lin-Wei covariance estimator to account for clustering of multiple periods of observations within persons. All multivariable models were adjusted for age, sex, body mass index, baseline CVD, systolic blood pressure, use of antihypertensive treatment, current smoking, and prevalent diabetes; a separate analysis additionally adjusted for LV cavity size. Covariates were selected on the basis of review of published data and clinical judgment of their probable associations with LVEF and the outcomes of HF and death, as well as on availability of these covariates in FHS examinations. Furthermore, we conducted several sensitivity analyses to evaluate for consistency with our primary results: using propensity score matching for CVD risk factor variables included in multivariable analysis, excluding patients with prevalent MI, and accounting for clustered observations among participants. Restricted penalized cubic splines were fitted to assess the linearity of the relationships between continuous LVEF and the outcomes. Statistical significance was considered at 2-tailed $p \leq 0.05$. However, in light of multiple significance tests of association, one should interpret modest p values ($0.005 < p < 0.05$) as denoting modest associations. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

PREVALENCE AND CORRELATES OF BORDERLINE LVEF IN THE STUDY SAMPLE. Online Figure 2 displays the distribution of LVEF in our study sample. The prevalence of LVEF categories was as follows: <50%: 1.6%; 5% to 55%: 3.5%; and >55%: 94.9%. The characteristics of participants with an LVEF of 50% to 55% in comparison with groups with an LVEF <50% and an LVEF >55% are presented in **Table 1**. Participants in whom LVEF assessment was unavailable had a greater burden of CVD risk factors but a prevalence of MI similar to that of participants with available echocardiograms (Online Table 2). The proportions of mean prevalence of CVD, MI, and diabetes, and brain natriuretic peptide level were intermediate in participants with an LVEF of 50% to 55%

TABLE 1 Demographic and Clinical Characteristics by LVEF Category

	LVEF (%)			
	<50 (n = 164)	50–55 (n = 363)	>55 (n = 9,743)	p Value
Age, yrs	61 ± 13	57 ± 13	60 ± 12	<0.0001
Male	128 (78)	216 (60)	4078 (42)	<0.0001
BMI, kg/m^2	26.9 ± 4.7	27.6 ± 4.5	27.0 ± 4.8	0.07
Prevalent CVD	74 ± 45	62 ± 17	1,086 ± 11	<0.0001
Prevalent MI	45 (27)	23 (6)	262 (3)	<0.0001
SBP, mm Hg	132 ± 19	133 ± 20	130 ± 20	0.01
DBP, mm Hg	77 ± 11	79 ± 10	76 ± 10	<0.0001
Hypertension	96 (59)	174 (48)	4,594 (47)	0.015
Hypertension treatment	68 (41)	87 (24)	3,066 (32)	0.0002
Diuretic agent use	23 (14)	49 (14)	1,460 (15)	0.69
Aspirin use*	64 (40)	110 (32)	2,537 (30)	0.026
Lipid-lowering therapy	36 (22)	40 (11)	1,544 (16)	0.0042
Diabetes	28 (17)	42 (12)	739 (8)	<0.0001
Smoking	34 (21)	74 (20)	1,588 (16)	0.048
LVEDD, cm	5.4 ± 0.8	5.0 ± 0.5	4.8 ± 0.5	<0.0001
BNP, pg/ml	54.3 (39.0)	33.1 (42.7)	15.0 (20.0)	<0.0001

Values are mean ± SD or n (%). *Data on aspirin use were not available for original cohort examination 16.

BMI = body mass index; BNP = brain natriuretic peptide; CVD = cardiovascular disease (coronary artery disease, myocardial infarction, angina, cerebrovascular accident, or transient ischemic attack); DBP = diastolic blood pressure; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure.

compared with participants with an LVEF <50% and an LVEF >55% (Table 1). Male sex, prevalent CVD, and higher blood pressure were associated with greater odds of having a borderline, compared with a normal, LVEF, whereas higher mean age and use of antihypertensive medications were inversely associated with a borderline LVEF (Table 2).

INCIDENCE OF COMPOSITE OUTCOME (HF/ALL-CAUSE MORTALITY) AND HEART FAILURE BY LVEF CATEGORY. The composite primary outcome (HF or death) occurred in 1,255 (12%) participants (cumulative incidence per LVEF group shown in Table 3 and Figure 1). Participants with an LVEF of 50% to 55% had an age- and sex-adjusted composite event rate of 0.24 per 10 years of follow-up. These event rates were intermediate between corresponding events in those participants with LVEF <50% and LVEF >55%. The adjusted hazard ratios for the primary outcome for the groups with an LVEF<50% and an LVEF of 50% to 55%, as compared with the referent group with an LVEF >55%, are shown in Table 4. Participants with a borderline LVEF had a greater risk of the composite outcome in all models compared with participants with an LVEF >55%. In analyses stratified by examination and prevalent MI, we observed similar, slightly higher hazard ratios for the composite outcome in all LVEF groups compared with the referent (Online Table 3). Participants with an unavailable LVEF had a greater risk of HF/death than did participants with an available LVEF (age- and sex-adjusted HR: 1.45; 95% confidence interval [CI]: 1.33 to 1.57; p < 0.0001; multivariable HR: 1.30; 95% CI: 1.19 to 1.42; p < 0.0001).

On follow-up, new-onset HF occurred in 355 (3.5%) participants. Table 3 and Figure 2 show the cumulative incidence of HF according to baseline LVEF category. The HF event rate in participants with a borderline LVEF was 0.13 per 10 years follow-up, which was intermediate between those with reduced LVEF and normal LVEF. Participants with an LVEF of 50% to 55% had a >2-fold increased risk for HF compared with those with an LVEF >55% in all models (Table 4). Similar results were seen in analyses stratified by examination and prevalent MI (Online Table 3). The addition of brain natriuretic peptide to multivariable models also yielded similar results (Online Table 4).

Because LVEDD is associated with CVD, we examined the relations of LVEDD in our models. LVEDD was associated with HF/mortality and HF in multivariable-adjusted models not including LVEF as a covariate (for HF/mortality, HR:1.33; 95% CI:

TABLE 2 Clinical Correlates of Borderline LVEF

	Odds Ratio (95% CI)	p Value
Age, per 10-yr increment	0.73 (0.65–0.82)	<0.0001
Women	0.57 (0.46–0.71)	<0.0001
Prevalent CVD	2.13 (1.56–2.91)	<0.0001
Diabetes	1.72 (1.21–2.45)	0.003
SBP, per 20-mm Hg increment	1.22 (1.04–1.43)	0.013
DBP, per 10-mm Hg increment	1.18 (1.03–1.36)	0.022
Hypertension treatment	0.63 (0.48–0.83)	0.001

Odds ratios are presented in relation to LVEF >55% group (referent).

CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

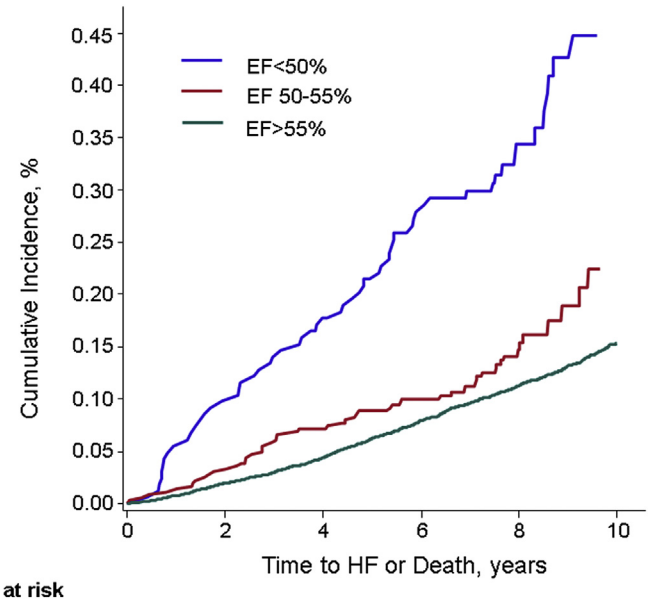
TABLE 3 Age- and Sex-Adjusted Occurrence of Outcomes

	HF or Death (n = 1,255)		HF (n = 355)	
LVEF (%)	Events, n	Incidence Rate, per 10-yr Follow-Up	Events, n	Incidence Rate, per 10-yr Follow-Up
<50	62	0.37 (0.27–0.44)	29	0.23 (0.12–0.32)
50–55	58	0.24 (0.16–0.31)	24	0.13 (0.05–0.19)
>55	1,135	0.16 (0.15–0.18)	302	0.05 (0.04–0.06)

Incidence rate, per 10-yr follow up, n (95% CI).

HF = heart failure; LVEF = left ventricular ejection fraction.

FIGURE 1 Cumulative Incidence of the Composite Primary Outcome (HF or Death) Among Left Ventricular EF Groups <50%, 50% to 55%, and >55%



No. at risk						
EF<50%	164	148	134	108	61	17
EF 50-55%	363	352	330	304	131	41
EF >55%	9743	9514	8530	7048	4487	1404

The incidence among participants with a left ventricular ejection fraction (EF) of 50% to 55% was intermediate between groups with left ventricular EF <50% and >55%. HF = heart failure.

1.18 to 1.50; p < 0.0001; for HF, HR: 2.25; 95% CI: 1.81 to 2.79; p < 0.0001), but inclusion in models including LVEF group only modestly attenuated the association of LVEF with the outcomes (Online Table 5).

TABLE 4 Hazard Ratios for Outcomes by Categorical and Continuous LVEF

	Model 1		Model 2	
LVEF (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
HF or death (n = 1,255 events)				
<50	2.35 (1.79–3.08)	<0.0001	2.01 (1.53–2.64)	<0.0001
50-55	1.46 (1.12–1.91)	0.0048	1.37 (1.05–1.80)	0.023
>55	Referent		Referent	
Continuous*	1.14 (1.10–1.18)	<0.0001	1.12 (1.07–1.16)	<0.0001
HF (n = 355 events)				
<50	3.38 (2.23–5.12)	<0.0001	2.84 (1.87–4.31)	<0.0001
50-55	2.25 (1.48–3.42)	0.0002	2.15 (1.41–3.28)	0.0004
>55	Referent		Referent	
Continuous*	1.26 (1.18–1.35)	<0.0001	1.23 (1.15–1.32)	<0.0001

Analyses stratified by cohort and by prevalent myocardial infarction. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, body mass index, baseline cardiovascular disease, smoking, diabetes, systolic blood pressure, and history of hypertension treatment. *HR per 5% decline in LVEF.

CI = confidence interval; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction.

Among participants in whom HF developed, the prevalence of HFPEF, HFREF, and interim MI are presented in Table 5. Of the participants with a baseline LVEF of 50% to 55% in whom HF developed and in whom LVEF was available, HFPEF developed in one-third, whereas HFREF developed in nearly two-thirds, a prevalence intermediate between those with an LVEF <50% and >55%. Interim MI (between echocardiography and follow-up) occurred in 78 (22%) participants in whom HF developed: n = 7 (24%) among those with a baseline LVEF <50%; n = 2 (8%) among those with an LVEF of 50% to 55%; and n = 69 (23%) among those with an LVEF >55%.

RISK OF OUTCOMES ACCORDING TO CONTINUOUS LVEF. In multivariable-adjusted analyses, every 5% decline in LVEF (modeled as a continuous variable) was associated with a 12% and 23% increase in the risk for the composite outcome and HF, respectively (Table 4). Splines revealed a nearly linear relationship of the risk of both the composite outcome and HF with decreasing LVEF (Figures 3 and 4). Results of tests for nonlinearity of these associations were not statistically significant (p = 0.28 for HF or death; p = 0.11 for HF).

SECONDARY ANALYSES USING BIPLANE SIMPSON'S LVEF. LVEF calculated by the de Simone and biplane Simpson methods correlated well (Pearson correlation 0.82; p < 0.0001) with good agreement (94% of observations falling within ±5%) (Online Figure 3). The weighted kappa statistic for categorical LVEF between the de Simone and biplane methods was 0.64, indicating very good agreement between the 2 methods.

HF or mortality occurred in 225 of 2,315 (10%) of FHS offspring participants. A borderline LVEF was associated with a >2-fold risk of HF/mortality (HR: 2.15; 95% CI: 1.04 to 4.45; p = 0.04). Each 5% decrement in LVEF was associated with a 17% risk of the composite outcome (p = 0.0004). There were 78 HF events. In logistic regression analyses, a trend toward risk of HF was seen, but it was not statistically significant (HR: 2.61; 95% CI: 0.91 to 7.50; p = 0.075). However, every 5% lower LVEF was associated with a 29% greater risk of HF (95% CI: 1.13 to 1.47; p = 0.0001).

EXAMINATION FOR SEX-INTERACTION AND SENSITIVITY ANALYSES. We did not observe effect modification by sex for either the composite outcome of HF/mortality or HF (p = 0.60 and p = 0.10, respectively). In sensitivity analyses using propensity-score matching, similar results were observed (Online Table 6). In additional sensitivity analyses excluding participants with prevalent MI and accounting for clustered

observations within participants, results were similar (data not shown).

DISCUSSION

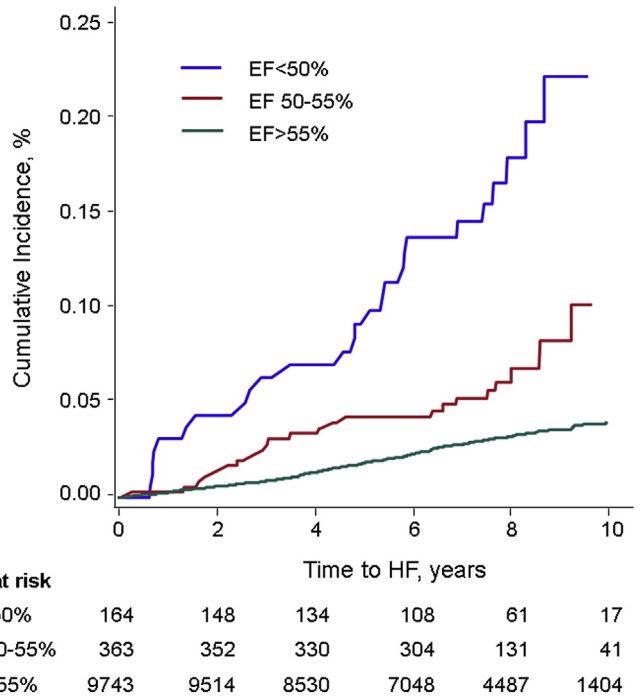
Whereas a mildly reduced LVEF is associated with adverse outcomes (6-8,25), the prognosis in persons with a borderline LVEF is unclear (9). In our large community-based sample, participants with a borderline LVEF had risks of adverse outcomes intermediate between those with an LVEF <50% and those with an LVEF >55%. We observed a graded inverse relationship between continuous LVEF and risk of HF and death. This suggestion of better prognosis with greater LVEF calls into question guidelines that define normal LVEF using thresholds along a continuum, and it is an area for future investigation. Our findings suggest that persons with a borderline LVEF have a worse prognosis than do persons with normal LVEF >55% and should not be considered "normal." Participants with an unavailable LVEF had the greatest risks for HF or death even after accounting for their greater prevalence of CVD risk factors, thus potentially highlighting the role of non-CVD causes of morbidity and mortality.

CHARACTERISTICS OF THE BORDERLINE LVEF GROUP. The prevalence of HFPEF and of HFREF at follow-up among participants with a baseline LVEF of 50% to 55% was intermediate between participants with an LVEF <50% and those with an LVEF >55%. The cause of HF in participants with borderline LVEF is unclear, but it cannot be explained as a consequence of MI, which occurred in a very small proportion of the participants in whom HF developed. In contrast, among those with LVEF <50%, development of symptomatic HF may be more attributable to ischemic events. Our findings are consistent with earlier reports suggesting that preclinical LV systolic dysfunction may progress to clinical HF along a continuum of incrementally lower LVEF, with possible neurohormonal derangements that may lead to adverse changes in the cellular and extracellular environment (6,26-29).

IMPLICATIONS OF SMALL DECREMENTS IN LVEF. Previous findings suggested that 3.0% to 7.3% of the population has asymptomatic LV systolic dysfunction (6,8), mostly mild LV systolic dysfunction (LVEF 45% to 54%). We observed a 3.5% prevalence of an LVEF of 50% to 55% that reflects a small but significant proportion of the general population. We noted a significantly increased risk for both HF and death with every 5% decline in LVEF. Whereas a 5% decrement in LVEF may seem to represent a small differential change, the implications at a population level may be large. For example, a 5% difference in LVEF represented a difference between LVEF quartiles in our sample. Thus, our findings may affect a significant proportion of the general population.

COMPARISON WITH PREVIOUS STUDIES AND IMPACT OF OUR FINDINGS. Even a mildly decreased LVEF in asymptomatic persons is associated with HF

FIGURE 2 Cumulative Incidence of HF Among Left Ventricular EF Groups <50%, 50% to 55%, and >55%



The incidence among participants with a left ventricular ejection fraction (EF) of 50% to 55% was intermediate between groups with left ventricular EF <50% and >55%. HF = heart failure.

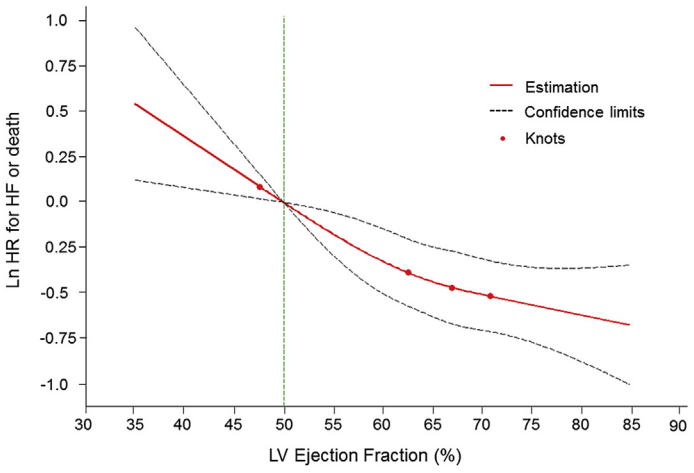
TABLE 5 Type of HF Developed and Prevalence of Interim MI Among Participants With HF, by Baseline LVEF Category*

Baseline LVEF (%)	HFPEF (n = 125)	HFREF (n = 179)	Uncategorized HF (n = 51)	Interim MI on Follow-Up (n = 78)
<50 (n = 29)	2 (7%)	26 (90%)	1 (3%)	7 (24%)
50-55 (n = 24)	8 (33%)	15 (63%)	1 (4%)	2 (8%)
>55 (n = 302)	115 (38%)	138 (46%)	49 (16%)	69 (23%)

Values are n (%). *Some HF cases were not differentiated into HFREF or HFPEF because of lack of echocardiographic evaluation proximate to the HF episode.

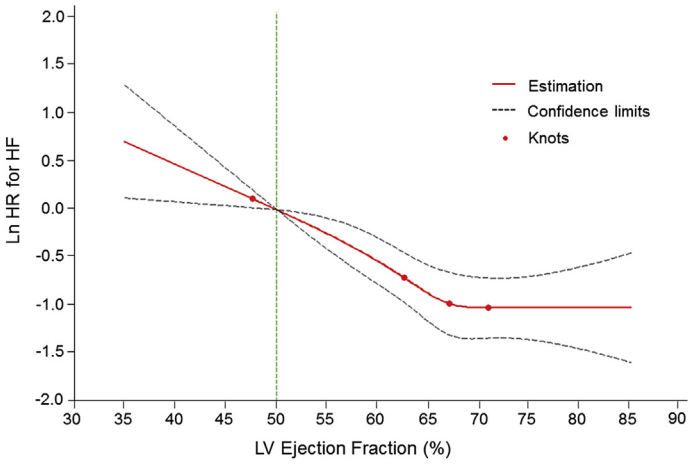
HF = heart failure; HFPEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

FIGURE 3 Multivariable-Adjusted Spline Modeling the Relationships of LV Ejection Fraction With the Risk of the Composite Primary Outcome (HF or Death)



A continuous, nearly linear relationship was seen between left ventricular (LV) ejection fraction and the combined outcome. The result of a test of nonlinearity was nonsignificant ($p = 0.28$). The spline was adjusted for age, sex, body mass index, baseline cardiovascular disease, smoking, diabetes, systolic blood pressure, and history of antihypertensive therapy. Knots were placed at the 1, 25, 50, and 75th percentile of LV ejection fraction. HF = heart failure; HR = hazard ratio; Ln = natural logarithm.

FIGURE 4 Multivariable-Adjusted Spline Modeling the Relationships of Ejection Fraction With the Risk of New-Onset HF



A continuous relationship was seen between left ventricular (LV) ejection fraction and the outcome of heart failure (HF). The result of a test of nonlinearity was nonsignificant ($p = 0.11$). The spline was adjusted for age, sex, body mass index, baseline cardiovascular disease, smoking, diabetes, systolic blood pressure, and history of antihypertensive therapy. Knots were placed at the 1, 25, 50, and 75th percentile of LV ejection fraction. HR = hazard ratio; Ln = natural logarithm.

and mortality (6-8,25,30). To our knowledge, the long-term prognosis of persons with a borderline LVEF is uncertain. Our finding of a risk for incident HF and death intermediate between LVEF <50% and >55% is consistent with earlier studies and extends the findings to a large population whose members currently may not receive attention because of their nearly normal LVEF. In addition, the rising risk of outcome events with progressively decreasing LVEF suggests a continuum of cardiovascular risk across the range of LVEF distribution. Clinically, a borderline LVEF may be referred to as "low-normal." However, our results suggest that this term for an LVEF of 50% to 55% may be misleading, and it may not convey the increased adverse risks associated with borderline LV systolic function.

Our findings are supported by consistency between our primary results and several secondary and sensitivity analyses including use of the biplane Simpson LVEF measurement, exclusion of persons with MI at baseline, accounting for clustered observations within participants, additional adjustment for LV cavity size, and propensity score matching. Substantial changes in imaging techniques and in CVD risk factor prevalence and treatment have evolved over the 3 decades encompassed in this study. Nevertheless, our results comparing participants within the same examination cycle (stratification by examination status and MI) were similar, albeit stronger, than results of our primary analyses, thus strengthening our conclusions. In addition, we examined for and did not observe effect modification by sex in these associations.

The optimal therapy, if any, for patients with a borderline LVEF of 50% to 55% remains uncertain. Currently, the borderline group represents persons who, under current guidelines, do not merit medical surveillance or therapy for HF prevention compared with persons with an LVEF<40%. The absolute event rates in this group are low and would preclude a randomized controlled clinical trial targeting this group to define optimal management strategies, beyond aggressive control of prevalent CVD risk factors.

STUDY LIMITATIONS. The FHS cohorts represent large, community-based samples in which echocardiographic measurements have been well validated and participants are under regular surveillance for the detection of events. In primary analyses, we used the method of de Simone for the estimation of LVEF that has been applied in numerous clinical studies (16-18); intercorrelation and intracorrelation measures of the echocardiographic measures were

excellent (31). Although this method assesses change in LV diameter at the base, it can overestimate or underestimate LVEF if regional wall motion abnormalities exist in the apical or basal regions, respectively. However, these misclassification errors would likely have biased our findings toward the null hypothesis of no association of borderline LVEF with the risk of developing outcome events. Furthermore, we observed similar results using the biplane Simpson LVEF calculation, and our data suggest very good agreement between the de Simone and biplane Simpson methods of LVEF calculation.

LV diastolic dysfunction is a feature of HF, both HFPEF and HFREF. We were unable to evaluate the separate and distinct contribution of diastolic dysfunction to HF because serial diastolic function parameters were unavailable at the baseline examination we chose. However, it is often challenging to differentiate the extent to which clinical HF exacerbations result from diastolic, as compared with systolic, dysfunction in patients with HFREF. We assessed HF outcomes that included the spectrum of LVEF (both preserved and reduced LVEF subtypes). Future investigation may elucidate the extent to which diastolic dysfunction contributes to clinical HF and mortality in persons with a borderline LVEF.

Whereas our observations suggest greater risk for the borderline LVEF group in the population, the LVEF measures are less precise at the level of an individual patient. Future studies using modern imaging modalities with greater reproducibility may reduce measurement variability, increase the sample size with assessable LVEF, and validate our findings. However, our observed low absolute event rates necessitate a long follow-up period, and thus a similar study may not be feasible with newer echocardiographic methods at this time.

Finally, additional epidemiological considerations must be made. Although we included clinical risk factors for HF in our statistical models, we cannot exclude residual confounding from unmeasured variables. Given the observational nature of this study, causal inferences cannot be made. We highlight that the majority of our sample consisted of middle-aged to older adults of Northern European descent, thus limiting generalizability to persons of other races or ethnicities. It would be of interest to evaluate the prognosis of a borderline LVEF in different population samples, including those identified in the clinical setting and in ethnically and racially diverse groups.

CONCLUSIONS

In our large community-based sample, a borderline LVEF of 50% to 55% was associated with significantly greater risks of death and HF compared with participants with a normal LVEF >55%. The risk of these outcomes increased linearly and incrementally with even small decrements in LVEF. Persons with an LVEF of 50% to 55% have an increased cardiovascular risk profile cross-sectionally and an elevated risk longitudinally, thereby suggesting that the term "low-normal" for this group may be potentially misleading. Further studies are necessary to confirm our findings and to determine the optimal surveillance strategy and treatment, if any, for members of the community who have an LVEF of 50% to 55%.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Risks of HF and mortality increase linearly and continuously with decreasing LV systolic function. Thus, persons with borderline LV systolic function should not be considered to have the same prognosis as persons with normal systolic function.

TRANSLATIONAL OUTLOOK: Future studies using more contemporary imaging modalities should be considered to determine the optimal management strategy for persons with borderline LV systolic function.

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KEY WORDS echocardiography, epidemiology, heart failure, left ventricular function

APPENDIX For supplemental tables and figures, please see the online version of this article.