The Association of Left Ventricular Ejection Fraction, Mortality, and Cause of Death in Stable Outpatients With Heart Failure

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OBJECTIVES	The aim of this study was to assess the prognostic importance of left ventricular ejection fraction (LVEF) in stable outpatients with heart failure (HF).
BACKGROUND	Although LVEF is an accepted prognostic indicator of prognosis in HF patients, the relationship of LVEF and mortality across the full spectrum of LVEF is incompletely understood.
METHODS	We examined the association of LVEF and outcomes among 7,788 stable HF patients enrolled in the Digitalis Investigation Group trial.
RESULTS	During mean follow-up of 37 months, mortality was substantial in all LVEF groups (range, LVEF ≤ 15%, 51.7%, LVEF > 55%, 23.5%). Among patients with LVEF ≤ 45%, mortality decreased in a near linear fashion across successively higher LVEF groups (LVEF < 15%, 51.7%; LVEF 36% to 45%, 25.6%; p < 0.0001). This association was present after multivariable adjustment, although the magnitude of this associated risk was reduced (LVEF ≤ 15%: hazard ratio [HR] 1.77, 95% confidence interval [CI] 1.48 to 2.11; LVEF 16% to 25%: HR 1.44, 95% CI 1.28 to 1.61; LVEF 26% to 35%: HR 1.10, 95% CI 0.98 to 1.28; LVEF 36% to 45%: referent). In contrast, mortality rates were comparable among patients with LVEF > 45% both before (LVEF 46% to 55%: 23.3%; LVEF > 55%: 23.5%; p = 0.25), and after multivariable adjustment (LVEF 46% to 55%: HR 0.92, 95% CI 0.77 to 1.10; LVEF > 55%: HR 0.88, 95% CI 0.71 to 1.09; LVEF 36% to 45%: referent). Patients with lower LVEF were at increased absolute risk of death due to arrhythmia and worsening HF, but these were leading causes of death in all LVEF groups.
CONCLUSIONS	Among HF patients in sinus rhythm, higher LVEFs were associated with a linear decrease in mortality up to an LVEF of 45%. However, increases above 45% were not associated with further reductions in mortality. (J Am Coll Cardiol 2003;42:736–42) © 2003 by the American College of Cardiology Foundation

The syndrome of heart failure (HF) occurs in patients with a full range of left ventricular ejection fraction (LVEF). Although LVEF is an accepted indicator of prognosis in HF patients, the relationship of LVEF, mortality, and cause of death across the full spectrum of LVEF is incompletely understood (1–11). Previous studies examining the prognostic value of LVEF have significant limitations, including that they were based on small numbers of patients (4,9,11,12) or limited to high-risk populations (1,5,9,10). More importantly, these studies failed to demonstrate how the association of LVEF and mortality changes across the full spectrum of LVEF because they did not include

substantial numbers of patients with preserved systolic function (1,3,4,6,7) or examined LVEF as a dichotomous rather than an ordinal or continuous variable (5–7).

Current American College of Cardiology/American Heart Association guidelines recommend the routine assessment of LVEF in HF patients to guide therapy, but fall short of defining a relationship between LVEF and prognosis (13). In addition, little information is available concerning specific causes of death in HF populations, particularly among patients with preserved systolic function. A more complete understanding of how the association of LVEF, mortality, and cause of death varies across the full LVEF spectrum would improve estimates of prognosis and may support the use of targeted interventions in specific populations.

The Digitalis Investigation Group (DIG) trial was a randomized clinical trial that enrolled a large number of stable HF patients and included patients with a full range of LVEF (14). The detailed information available on these patients provides an ideal opportunity to examine the association of LVEF, mortality, and cause of death among stable patients with HF and a full range of LVEF.

Abbreviations and Acronyms

BMI = body mass index
DIG = Digitalis Investigation Group
ERNA = equilibrium radionuclide angiography
HF = heart failure
LVEF = left ventricular ejection fraction
MI = myocardial infarction

METHODS

The DIG trial. The DIG trial was conducted to examine the effect of digitalis on mortality and hospitalization in HF patients (14,15). Patients with stable, clinically confirmed HF in sinus rhythm (n = 7,788) were randomized to digitalis or placebo at 302 centers in the U.S. and Canada. Randomization was stratified by both enrolling center and LVEF: patients with LVEF ≤ 45% (n = 6,800) were enrolled in the main arm of the trial, and patients with LVEF > 45% (n = 988) were enrolled in a parallel ancillary arm. Because the eligibility criteria and follow-up were otherwise identical, we combined data from both arms to include a full spectrum of LVEF.

LVEF determination. In the DIG trial, LVEF was measured in all patients before enrollment using either echocardiography, equilibrium radionuclide angiography (ERNA), or contrast ventriculography. The DIG investigators recorded a single value of LVEF in each patient and used LVEF measurements performed up to six months before enrollment unless the patient had an intervening event. If more than one technique had been used, angiographic and radionuclide techniques were deemed equally acceptable, and either was preferred to echocardiographic measures. For this analysis, patients were divided into six groups that demonstrated the association of LVEF and outcomes but retained enough patients in each group to make meaningful comparisons: LVEF ≤15%, 16% to 25%, 26% to 35%, 36% to 45%, 46% to 55%, and >55%.

Outcomes. We examined all-cause mortality, death due to arrhythmia, and death due to worsening HF over a median follow-up of 37 months. Cause of death was assigned by local investigators blinded to treatment assignment on the basis of chart review and interview of relatives (14,15).

Statistical analysis. We evaluated the association of LVEF and patient characteristics using chi-square trend analyses for categorical variables and Wilcoxon test for trend for continuous variables (16). We compared crude overall and cause-specific mortality rates across LVEF groups using global and test for trend chi-square analyses. Kaplan-Meier survival curves were plotted for each LVEF group and compared using log-rank test.

Multivariable analyses were conducted to determine whether other clinical characteristics confounded the association of LVEF and mortality. Candidate covariates were identified using a backward stepwise Cox proportional hazards model with an entry criterion of p = 0.1 and a retention criterion of p = 0.01. Independent predictors of mortality incorporated into multivariable analysis were age, gender, body mass index (BMI), HF etiology, New York Heart Association class, diabetes, radiologic evidence of pulmonary edema on admission or in the past, cardiothoracic ratio, blood pressure, creatinine, S3, rales, previous use of digitalis, angiotensin-converting enzyme inhibitors, diuretics, nitroglycerin, and study drug assignment.

We conducted two secondary analyses to confirm the robustness of LVEF's association with mortality. First, LVEF groups were replaced with a single continuous LVEF measure to assess the linearity of LVEF's association with mortality using fractional polynomial modeling (17). Second, the Cox proportional hazards multivariable analysis was repeated restricting the cohort to patients in whom LVEF was measured by ERNA. Statistical analyses were performed using SAS 8.02 (SAS Institute Inc., Cary, North Carolina) and Stata 7.0 (Stata Corporation, College Station, Texas).

RESULTS

Study sample. The LVEF was measured by ERNA (n = 5,074, 65.2%), left ventricular contrast angiography (n = 428, 5.5%), or two-dimensional echocardiography (n = 2,296, 29.4%). The use of these techniques was comparable across LVEF groups. Patients with lower LVEF were younger and a greater proportion were male compared with patients with higher LVEF. Patients with low LVEF had lower rates of hypertension and diabetes, as well as lower systemic blood pressures, BMI, and serum potassium. In contrast, rates of previous myocardial infarction (MI), ischemic HF, heart rates, and serum creatinine were higher among patients in lower LVEF groups (Table 1).

LVEF and crude mortality rates. The overall crude mortality rate was 33.5% with a 28.2% absolute difference between patients in the lowest and highest LVEF groups (LVEF ≤ 15%: 51.7%; LVEF > 55%: 23.5%; p < 0.001) (Fig. 1, Table 2). The association of LVEF and mortality changed across the full spectrum of LVEF. Among patients with LVEF < 45%, mortality rates increased in a near linear fashion across successively lower LVEF groups (LVEF < 15%: 51.7%; LVEF 36% to 45%: 25.6%; p < 0.001). In contrast, mortality rates were comparable for patients in LVEF groups above 45% (LVEF 46% to 55%: 23.3%; LVEF > 55%: 23.5%; p = 0.25). Each LVEF group below 45% was associated with shorter survival time (log-rank p < 0.001, Fig. 2), but the mortality of patients with LVEF 46% to 55% was not significantly different than that of patients with LVEF > 55% (log-rank p = 0.92). The results were similar when the analysis was restricted to patients with an LVEF measured by ERNA (data not shown).

LVEF as an independent predictor of mortality. After multivariable adjustment, lower LVEF values were independently associated with increased mortality among pa-

Table 1. Baseline Characteristics Stratified by LVEF

	Total (n = 7,788)	LVEF ≤ 15% (n = 567)	LVEF 16% to 25% (n = 2,118)	LVEF 26% to 35% (n = 2,477)	LVEF 36% to 45% (n = 1,638)	LVEF 46% to 55% (n = 593)	LVEF > 55% (n = 395)	p for Trend
Demographics								
Age (SD)	63.9 (10.9)	61.9 (10.6)	63.2 (11.1)	63.7 (11.0)	64.2 (10.7)	66.0 (10.3)	68.0 (10.2)	<0.01
Female (%)	24.7	16.9	19.0	21.8	29.4	33.9	52.2	<0.01
Black (%)	14.5	18.2	16.0	13.2	13.4	12.5	16.0	0.01
BMI (SD)	27.3 (5.4)	26.4 (4.9)	26.9 (5.2)	27.1 (5.2)	27.6 (5.3)	28.3 (5.5)	29.2 (7.1)	<0.01
Clinical history								
Failure on CXR (%)	60.0	66.0	62.9	59.3	56.8	56.2	59.7	<0.01
MI (%)	63.0	54.9	62.5	70.2	63.8	57.2	38.0	<0.01
Diabetes (%)	28.5	22.8	27.5	30.3	28.8	29.0	28.6	0.04
Hypertension (%)	47.2	40.4	43.3	44.5	51.0	55.5	66.1	<0.01
Ischemic HF (%)	68.8	61.7	67.3	74.9	71.6	64.6	44.1	<0.01
Signs/symptoms on enrollment								
Rales (%)	16.7	23.5	19.7	15.3	13.2	16.2	14.9	<0.01
S3 (%)	23.7	42.5	30.5	23.5	16.6	11.1	9.4	<0.01
Angina (%)	27.2	23.5	24.6	28.1	28.8	30.2	29.1	<0.01
Heart rate: mean (SD)	78.4 (12.2)	82.2 (13.2)	80.3 (12.9)	77.8 (12.3)	76.9 (12.2)	75.8 (12.3)	75.8 (11.5)	<0.01
BP (mm Hg)								
Systolic (SD)	127.3 (20.5)	116.7 (17.5)	123.1 (19.6)	126.6 (19.6)	131.3 (19.9)	135.5 (20.4)	140.6 (22.2)	<0.01
Diastolic (SD)	75.1 (11.3)	74.0 (11.3)	74.4 (11.4)	74.5 (11.1)	76.4 (11.1)	76.9 (11.0)	76.7 (11.9)	<0.01
HF duration (months)	29.7	30.7	30.6	30.1	29.5	27.0	26.2	<0.01
NYHA class: III/IV (%)	31.3	52.2	38.5	29.2	23.6	19.6	25.8	<0.01
Laboratory or X-ray data								
Failure on CXR (%)	14.2	22.4	18.0	13.4	10.3	9.8	10.9	<0.01
CT ratio (%)	53.1	56.4	54.5	52.6	52.0	51.4	52.1	<0.01
Serum creatinine (mg/dl)	1.28	1.31	1.31	1.28	1.26	1.26	1.25	<0.01
LVEF technique								
ERNA	65.2	63.0	64.3	64.2	66.1	70.2	67.6%	0.05
Echocardiography	29.4	32.3	31.1	29.5	27.7	25.6	27.6%	0.07
Contrast ventriculography	5.5	4.8	4.7	6.3	6.3	4.2	4.8%	0.03
Medication on admission								
Digoxin (%)	43.2	52.6	47.0	44.0	38.6	33.9	37.2	<0.01
Diuretics (%)	81.5	90.7	86.3	79.5	76.1	79.1	82.3	<0.01
ACE inhibitor (%)	93.4	95.1	96.1	94.4	92.1	87.0	85.1	<0.01
Nitrates (%)	42.2	42.9	42.3	44.0	41.0	39.6	39.0	0.07

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CT = cardiac–thoracic; CXR = chest X-ray; ERNA = equilibrium radionuclide angiography; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SD = standard deviation.

tients with LVEF ≤ 45%, but the magnitude of the association was reduced (Table 3). The mortality observed in LVEF groups above 45% remained comparable.

LVEF and cause of death. Worsening HF and arrhythmia were the leading specific causes of death (Table 2). Deaths due to arrhythmias, worsening HF, and other cardiac causes were more frequent among patients in lower LVEF groups (p < 0.0001 for trend). Deaths due to non-cardiovascular causes were more frequent among patients with LVEF > 45% (p = 0.046 for trend). Worsening and arrhythmias HF were leading causes of death in all LVEF groups, including patients with relatively preserved systolic function (Fig. 3).

DISCUSSION

Previous investigators have attempted to characterize the relationship between LVEF and mortality in HF patients, with inconsistent results (3,4,6–9,11,12,18–23). Our findings help resolve the conflicting findings of previous studies and provide several important insights into the association of LVEF and mortality.

In contrast to previous investigations, we demonstrated that the association of LVEF and mortality changes substantially across the full spectrum of LVEF. Studies that dichotomized LVEF (6,7,23) may have obscured the dynamic nature of this association. Those that examined LVEF as a continuous variable, several did not describe the association of LVEF and mortality across the full spectrum of LVEF (1,2). The remaining studies had significant limitations in that they were small (9,11), limited to patients with ischemic HF (10), or included few patients with preserved LVEF (3). Although our analysis does not identify the precise inflection point above which further increases in LVEF are not associated with lower mortality, it strongly suggests that the transition occurs in the range of 40% to 50%.

Previous investigators have concluded that the prognostic utility of LVEF declines once its value falls below 25% (13,24). In contrast, we found that the crude mortality of patients with LVEF ≤ 15% was 10% higher than that of patients with an LVEF of 16% to 25%, and within this
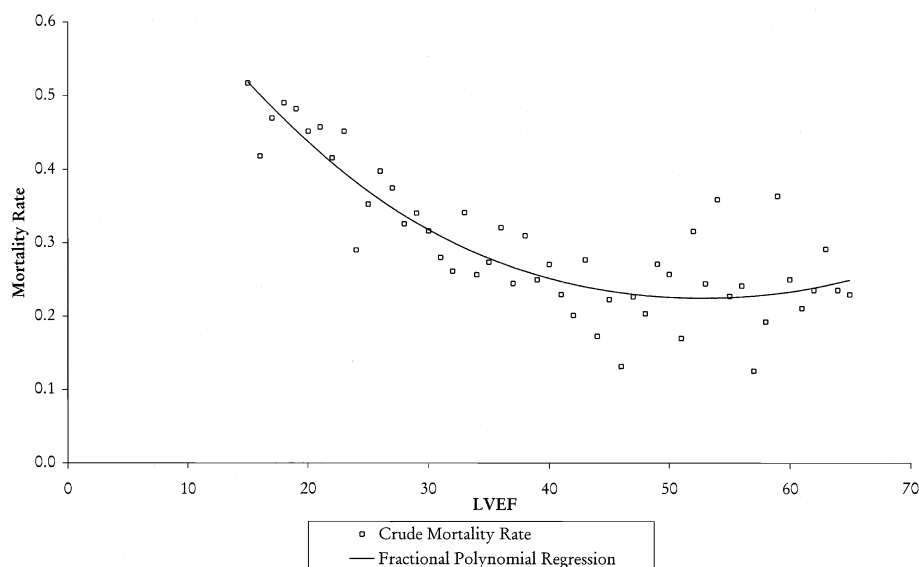
Figure 1. Linear trend for left ventricular ejection fraction (LVEF) as a continuous variable and unadjusted all-cause mortality. Each point represents the mortality rate associated with each LVEF point.

interval higher measures of LVEF were associated with a linear decline in mortality (Fig. 1). After multivariable adjustment, the difference between these groups was not statistically significant. However, the adjusted hazard ratio of patients with LVEF ≤ 15% was 23% higher than that of patients with LVEF 16% to 25%, and the magnitude of this difference was similar to that observed between other LVEF groups. Accordingly, our findings suggest that the graded and continuous relationship between LVEF and mortality is present even among patients with severely depressed systolic function.

In this large group of patients with established HF (mean previous duration of HF 2.5 years), the mortality rates associated with individual LVEF groups were stable over time. We found no evidence of an increased early hazard among patients with severe LV dysfunction, nor was there an indication of increased late mortality in any LVEF group. Our findings would suggest that on average, LVEF

is associated with a constant, fixed mortality risk. As such, survival for several years with a lower LVEF may not necessarily indicate a better future prognosis.

We found the relative risk associated with LVEF to be modest in comparison with the MI experience, as shown by the less than threefold difference in mortality rates between patients in the lowest and highest LVEF groups. In MI populations, LVEF is associated with a more than 10-fold relative difference in mortality rates (25). The difference in the prognostic significance of LVEF in these cohorts is due to the mortality observed in HF patients with preserved LVEF. Thus, our findings emphasize the substantial mortality risk associated with the syndrome of HF irrespective of LVEF.

Finally, the strength of the association of LVEF and mortality was reduced by multivariable adjustment, indicating that a substantial portion of the increased risk of death observed in patients with systolic dysfunction could be

Table 2. Crude Mortality and Cause of Death

	Total (n = 7,788)		LVEF ≤ 15% (n = 567)		LVEF 16% to 25% (n = 2,118)		LVEF 26% to 35% (n = 2,477)		LVEF 36% to 45% (n = 1,638)		LVEF 46% to 55% (n = 593)		LVEF > 55% (n = 395)		p for Trend
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	
Overall mortality	2,606	33.5	293	51.7	884	41.7	778	31.4	420	25.6	138	23.3	93	23.5	<0.01
Cause of death															
Cardiovascular	2,052	26.3	265	46.7	730	34.5	597	24.1	298	18.2	100	16.9	62	15.7	<0.01
Arrhythmic	583	7.5	79	13.9	217	10.2	155	6.3	96	5.9	25	4.2	11	2.8	<0.01
Worsening HF	907	11.6	148	26.1	333	15.7	268	10.8	94	5.7	34	5.7	30	7.6	<0.01
Other cardiac	451	5.8	35	6.2	150	7.1	143	5.8	77	4.7	33	5.6	13	3.3	0.00
Stroke	57	0.7	1	0.2	17	0.8	17	0.7	15	0.9	3	0.5	4	1.0	0.36
Embolism	18	0.2	0	0.0	7	0.3	3	0.1	6	0.4	1	0.2	1	0.3	0.67
Other vascular	36	0.5	2	0.4	6	0.3	11	0.4	10	0.6	4	0.7	3	0.8	0.07
Noncardiovascular	410	5.3	20	3.5	107	5.1	129	5.2	99	6.0	29	4.9	26	6.6	0.05
Unknown	144	1.8	8	1.4	47	2.2	52	2.1	23	1.4	9	1.5	5	1.3	0.15

HF = heart failure; LVEF = left ventricular ejection fraction.
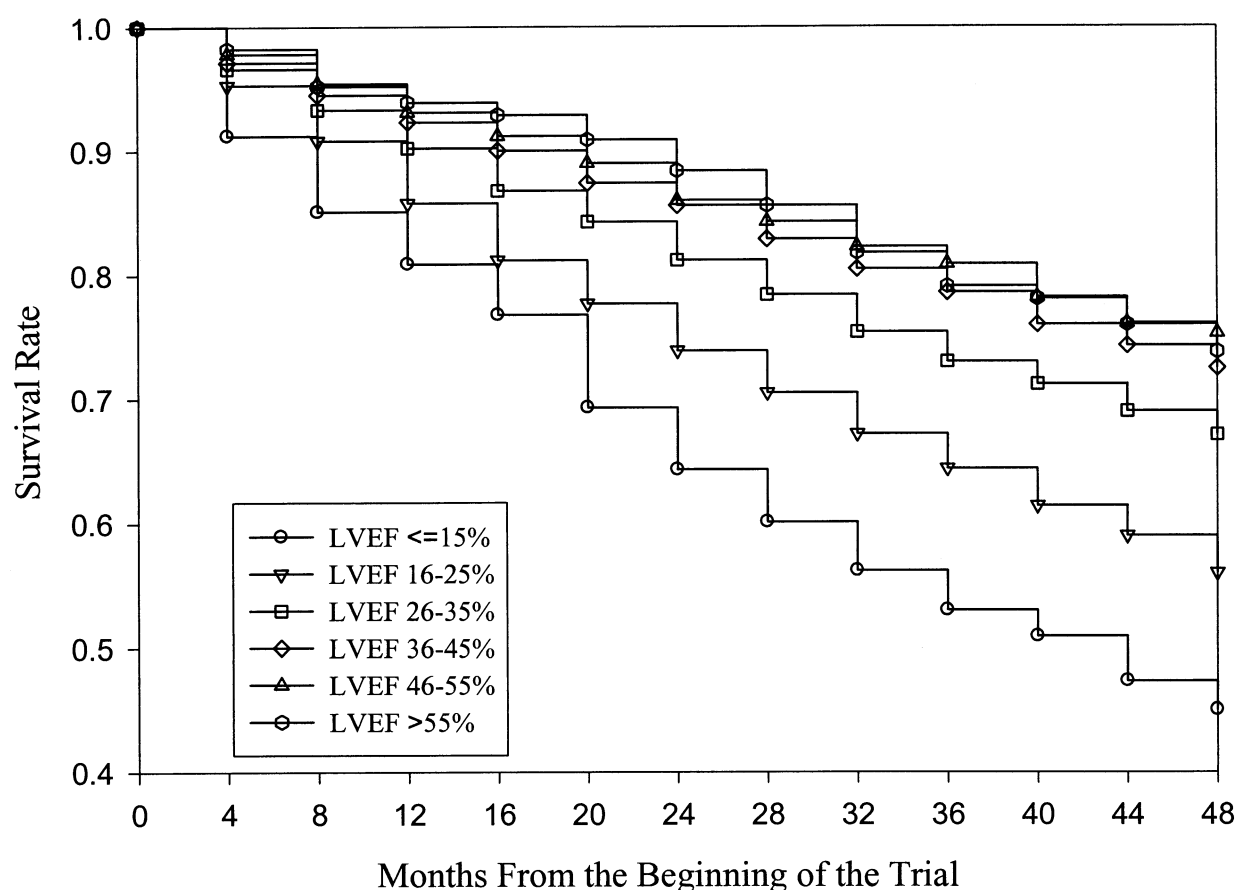
Months	0	4	8	12	16	20	24	28	32	36	40	44	48
LVEF <=15%	567	517	479	455	431	388	358	335	313	263	218	173	134
LVEF 16-25%	2118	2018	1918	1808	1713	1637	1554	1480	1407	1216	1025	830	622
LVEF 26-35%	2477	2393	2309	2227	2139	2076	1994	1920	1844	1619	1379	1109	865
LVEF 36-45%	1638	1591	1548	1511	1472	1427	1393	1348	1305	1123	964	753	584
LVEF 46-55%	593	580	565	551	540	527	509	499	487	405	325	247	186
LVEF >55%	395	388	376	371	367	359	349	338	323	271	229	176	135

Figure 2. Kaplan-Meier survival curves stratified by left ventricular ejection fraction (LVEF) group.

explained by other differences between groups. Although LVEF is a strong independent predictor of mortality in HF patients, the prognostic value of LVEF should be interpreted in the context of other established risk factors.

Our study also adds insight into the prognosis of patients with HF and preserved systolic function that may account for up to half of all hospital admissions for HF (12,26–29).

Although these patients have lower mortality compared with patients with systolic dysfunction, they are at increased risk of death compared with patients without HF (12,22,30). The annual mortality reported in previous studies ranges from 1.3% to 17.5% (12,27–35), but the variation in these estimates appears mainly due to differences in patient characteristics. We found that patients with rela-

Table 3. LVEF and Mortality: Multivariable Analysis

	LVEF ≤ 15%	LVEF 16% to 25%	LVEF 26% to 35%	LVEF 36% to 45%*	LVEF 46% to 55%	LVEF > 55%
Unadjusted	2.66 (2.26, 3.14)	1.85 (1.66, 2.07)	1.28 (1.14, 1.43)	1.00	0.88 (0.73, 1.05)	0.88 (0.71, 1.08)
Adjusted: [1]	2.66 (2.25, 3.14)	1.82 (1.63, 2.04)	1.26 (1.12, 1.41)	1.00	0.85 (0.71, 1.02)	0.82 (0.66, 1.02)
Adjusted: [2]	2.03 (1.71, 2.41)	1.56 (1.39, 1.75)	1.15 (1.02, 1.29)	1.00	0.87 (0.73, 1.05)	0.83 (0.67, 1.04)
Adjusted: [3]	1.84 (1.54, 2.18)	1.47 (1.30, 1.65)	1.13 (1.01, 1.26)	1.00	0.91 (0.76, 1.09)	0.89 (0.71, 1.10)
Adjusted: [4]	1.77 (1.49, 2.11)	1.44 (1.28, 1.61)	1.10 (0.98, 1.28)	1.00	0.92 (0.97, 1.10)	0.88 (0.71, 1.09)

*Reference group: left ventricular ejection fraction (LVEF) 36% to 45%. [1] Demographics + History. [2] Demographics + History + Admission. [3] Demographics + History + Admission + Laboratory. [4] Demographics + History + Admission + Laboratory + Previous medications + Study drug assignment.
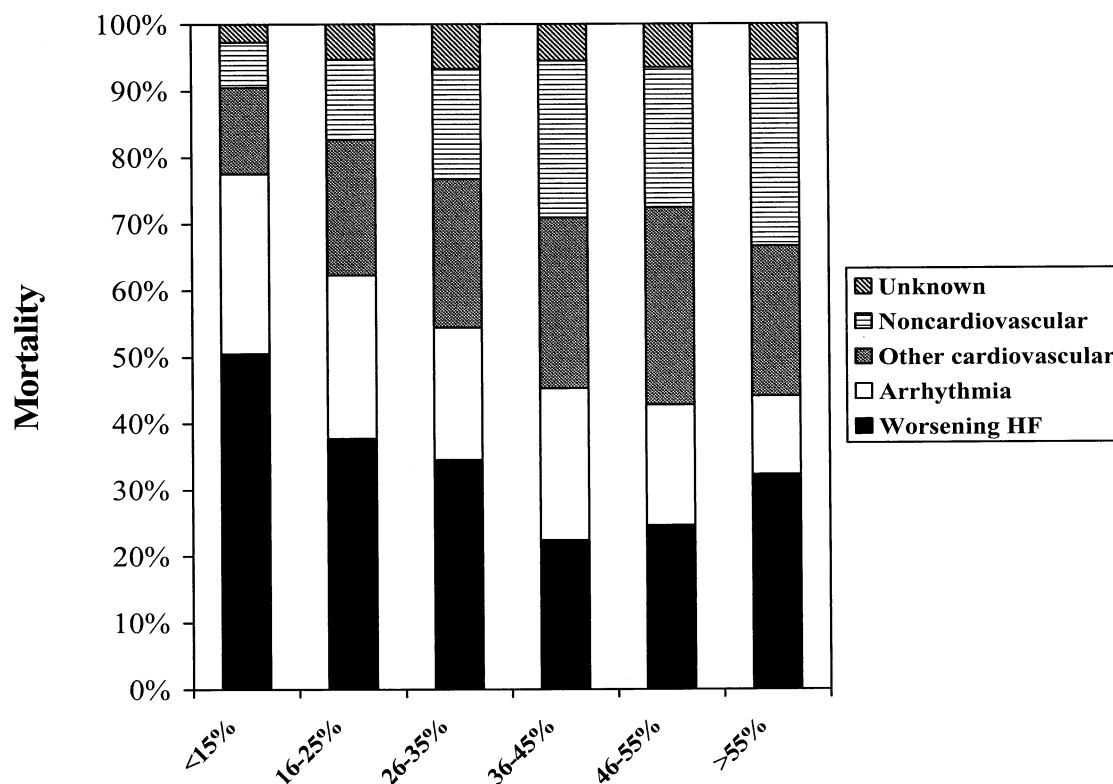
Figure 3. Proportion of death attributed to specific causes of death across left ventricular ejection fraction groups. HF = heart failure.

tively preserved systolic function had an average annual mortality of 5.8%, which is comparable to the 8.7% previously observed in the Framingham Study (27).

The causes of death in HF populations with preserved systolic function are also incompletely defined. Previous investigations have found these patients frequently die of cardiovascular causes (12,28–31), but these studies were small and employed variable classification schemes. Not unexpectedly, we found the incidence of specific causes of death varies with LVEF. Patients with LVEF ≤ 15% were four times more likely to die of either arrhythmia or worsening HF than patients with LVEF > 45%. Nevertheless, deaths due to arrhythmias and worsening HF were common among patients with LVEF > 45%. In addition, the high absolute rate of arrhythmic mortality suggests the need to develop strategies aimed at reducing the risk of lethal arrhythmias, including risk stratification, use of beta-blockers, and possibly consideration of implantable cardiac defibrillators in HF patients with higher LVEF than those previously enrolled in randomized trials. Although determining a specific cause of death in HF patients is difficult and may be prone to error (36), our results should serve as a basis for the design and implementation of strategies aimed at decreasing mortality in this understudied population.

Several aspects of our study merit further consideration. The DIG trial did not standardize the technique or interpretation of LVEF measurement. Because measurement techniques were similar across the LVEF groups, any

misclassification of LVEF would presumably have been evenly distributed and thus produced no net bias. Furthermore, our results were similar when we restricted our analysis to patients who had an ERNA-assessed LVEF. The DIG trial protocol did not specify measurement of functional capacity, such as peak oxygen capacity. In addition, since the completion of the DIG trial, increased use of beta-blockers and spironolactone in patients with LV systolic dysfunction might have narrowed the difference in mortality between HF patients with LVEF above and below 45%. Finally, patients in the DIG trial were younger and had fewer comorbidities than HF patients in observational cohorts (37,38). It is unclear if the association of LVEF and mortality would be similar in patients with additional comorbidities. Nevertheless, this is the largest study of stable HF patients to include a full spectrum of LVEF, and our results should serve as a viable estimate of risk conferred by LVEF until additional studies are completed.

In summary, our study demonstrates that the association of LVEF and mortality changes substantially across the full spectrum of LVEF. This information clarifies the role of LVEF in HF patients and will help clinicians provide better estimates of prognosis. In addition, understanding that arrhythmias and worsening HF contribute to substantial mortality observed in patients with HF with preserved LVEF may help target future interventions in this population.

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