Serial Changes in Left Ventricular Ejection Fraction and Outcomes in Outpatients With Heart Failure and Preserved Ejection Fraction

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Limited data exist on the course of left ventricle ejection fraction (LVEF) among outpatients with heart failure (HF) and preserved ejection fraction (HFpEF) and its impact on outcomes. We evaluated 322 consecutive outpatients with confirmed HF, LVEF >40%, no previous LVEF ≤40%, and no specific cardiomyopathies or primary right-sided or valvular heart disease. Median age was 73 years (interquartile range: 63 to 82); 57.1% were women, 50.3% White, and 45.0% Black; median LVEF was 55% (50% to 60%); and 45.6% had coronary artery disease. After a median of 37 months (32 to 38) and 4.5 follow-up echocardiograms (4 to 6) per patient, 11.4% of patients (95% confidence interval [CI] 5.2% to 17.7%) developed LVEF <40%. The average drop in LVEF among these patients was 19.4 units (95%CI 15.0 to 23.8) to an average LVEF of 30.3% (95%CI 27.4% to 33.2%). Baseline systolic blood pressure >130 mm Hg was associated with more LVEF decline. During follow-up, 50 patients died (3-year mortality 15.3%) and 67 additional patients were hospitalized for HF (3-year death plus HF hospitalization 35.6%). Development of LVEF <40% was subsequently followed by 5-fold higher mortality in time-updated models (adjusted HR 4.91; 95%CI 2.00 to 12.0; p = 0.001) and 3.5-fold higher rates of death or HF hospitalization (adjusted HR 3.70; 95%CI 1.67 to 8.19; p = 0.001). Interval coronary events were infrequent (10%) among patients with deteriorated LVEF. The impact of LVEF changes on outcomes was similar in White and Black patients. In conclusion, a proportion of patients with HFpEF will develop reduced LVEF over time. These patients have worse prognosis subsequently. **(Am J Cardiol 2019;124:729−735)**

Heart failure (HF) with reduced ejection fraction (HFrEF) is characterized by intense neurohormonal activation and responds to agents that block the neurohormonal axes.[1] Impaired left ventricular ejection fraction (LVEF), usually defined as ≤40%, clearly indicates reduced systolic function, and a lower LVEF within the HFrEF range is linearly associated with worse prognosis.[2] On the other hand, HF with preserved ejection fraction (HFpEF) has a diverse pathophysiology.[3] As a result, no proven therapies exist for HFpEF, with the potential exception of spironolactone.[3] To compound complexity, echocardiographic studies using ventricular mechanics have shown that a midrange (41% to 49%) and even preserved (≥50%) LVEF is not synonymous with normal systolic function, as many patients have reduced left ventricular longitudinal strain.[4,5] These patients are potentially vulnerable to deterioration of systolic function. In a prospective cohort study, 39% of patients with initial LVEF ≥50% presented with an LVEF of ≤50% on at least 1 follow-up visit over the next 3 years.[6] In another study, 1 out of 4 patients with initial midrange LVEF transitioned to HFrEF within 1 year and had worse prognosis.[7] However, there are still gaps in our knowledge on the prognostic value of LVEF trajectory in HFpEF. Data on the impact of unfavorable LVEF changes on mortality are limited,[6] and the impact on composite endpoints, which are common in clinical trials, has not been estimated. Also, no race-specific data have been reported to date. In the present study, we report (1) changes in LVEF in a racially diverse cohort of outpatients with HFpEF over a period of 3 years and (2) the impact of these changes on outcomes, including mortality and death-hospitalization composite endpoints. We also examined clinical factors that may help identify patients with HFpEF at higher risk for LVEF deterioration.

Methods

We used the International Classification of Disease, Clinical Modification (ICD-9-CM) 402.X1, 404.X1, 404.X3, and 428.XX codes, to identify all adult outpatients who received care for HF at Emory University between January 1, 2012 and April 15, 2012 by cardiologists, including HF specialists. The timeframe was selected to provide a minimum of 3 years of follow up. We individually reviewed medical records for verification of HF diagnosis based on the presence of symptoms and signs of HF accompanied by treatment for HF. We recorded LVEF at index visit and documented previous LVEF determinations. For this study, we defined preserved LVEF as current LVEF >40% and no

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previous LVEF ≤40%.[8] However, as HF with midrange LVEF is increasingly recognized as a HF subgroup with mixed characteristics, we do provide data for the subset of patients LVEF >50% separately. Patients with (1) specific cardiomyopathies, such as, hypertrophic, infiltrative, restrictive, and chemotherapy-induced; (2) complex congenital heart disease; (3) primary right-sided heart disease; (4) primary valvular disease; and (5) previous heart transplant or mechanical circulatory support were excluded. The study has been approved by the Institutional Review Board of Emory University.

Clinical data were collected through the Emory Electronic Medical Record system. For laboratory values, we extracted the last information available up to the index visit. We defined coronary artery disease as a history of acute myocardial infarction, acute coronary syndrome, or stable angina. Comorbidities, including hypertension, diabetes, atrial fibrillation, chronic lung disease, sleep apnea, cerebrovascular disease, depression, and dementia, were defined based on physician diagnosis and relevant therapy. We have previously reported in more detail the methods for assessment of clinical characteristics, conditions and comorbidities in this cohort.[9]

Outcomes data, including hospitalizations and death, were collected through Stony Brook Hospital Electronic Medical Records in 6 months for at least 3 years after the index date. For those who did not continue care with our system throughout the 3-year period, the last encounter was considered the last day of follow up. Hospitalizations and outpatient visits were individually reviewed and records of interim hospitalizations in outside centers were reviewed and recorded. Hospitalizations were classified, based on the primary diagnosis, into cardiovascular and noncardiovascular, with the former being further divided into HF-related and non−HF-related. In addition, to assess the potential impact of interval events on LVEF deterioration, we identified all hospitalizations with the following conditions as the primary reason: acute coronary syndromes, acute renal failure or worsening chronic renal dysfunction, diabetes complications (as a proxy for diabetes control), and cancer-related admissions (as a proxy for cancer treatments).

We used Cox proportional hazards to model composite time-to-event endpoints and Schoenfeld residuals to test for nonproportional hazards; the proportionality assumption was valid in all models. We considered the following variables in our models, based on known associations with outcomes, clinical interpretation, and previous work: age, sex, race (white, black, other), marital status, insurance status, body mass index, New York Heart Association functional class, history of hypertension, systolic blood pressure, diabetes mellitus, coronary artery disease, cerebral and peripheral vascular disease, sleep apnea, depression, dementia, chronic lung disease, atrial fibrillation, anemia cancer, serum albumin, and eGFR. To reach parsimonious adjustment models and avoid overfitting (because of the small number of events relatively to the number of covariates), we used backwards regression with bootstrapping (1000 replications per step). In a subgroup analysis we report changes in LVEF and outcomes for the subset of patients with baseline LVEF >50% and considering LVEF ≤50% during follow-up as a drop in LVEF. We compared interval events between LVEF deterioration groups as binary events (yes or no) using Fisher's exact chi-square as the number of events was relatively small for count-data analysis. We used STATA 14.1 (StataCorp LP, College Station, TX) for analyses.

Results

We identified 322 patients with echocardiographic follow-up (Table 1). Patients who had follow-up echocardiograms were more likely to have a history of structural cardiac surgery and less likely to have dementia; other characteristics were comparable to patients without follow-up echocardiograms (N = 123). Median (interquartile range) LVEF at baseline was 55% (50% to 60%) and mean (standard deviation) LVEF was 54.7% (6.4%). At baseline, LVEF was lower in men versus women (52.7% vs 56.1%; p <0.001), in those who had coronary revascularization (55.3% vs 53.8%; p = 0.042), and in implantable cardioverter defibrillator recipients (54.9% vs 50.9%; p = 0.019), although the number of the latter was small. Mean LVEF was higher among patients receiving calcium channel blockers (56.7% vs 53.5%; p <0.001). Lower diastolic blood pressure ($r = -0.15$; p = 0.015) and hemoglobin ($r = -0.16$; p = 0.003) were associated with higher LVEF.

Median follow-up was 37 months (32 to 38). During that period, patients underwent an average of 4.5 follow-up echocardiograms (minimum: 4, maximum: 6). By 36 months, 11.4% of patients (95%CI 5.2% to 17.7%; p <0.001 vs baseline) had developed LVEF <40% (p <0.001 for linear trend over time) (Figure 1). The time-averaged drop in LVEF from baseline in patients who developed LVEF <40% was 19.4% (95%CI 15.0% to 23.8%) and the time-averaged LVEF in these patients was 30.3% (95%CI 27.4% to 33.2%).

Among clinical characteristics presented in Table 1, only baseline systolic blood pressure was significantly associated with development of LVEF <40% in mixed-effects models. Patients with baseline systolic blood pressure >130 were more likely to develop LVEF <40% (p = 0.018 for interaction of systolic blood pressure with time) (Figure 2).

When analyzed as a continuous variable, LVEF declined by 0.47 % units per year (95%CI 0.07 to 0.87; p = 0.022) (Figure 3). By 36 months, the average decline in LVEF was 1.9 % units (95%CI 0.2 to 3.7; p = 0.028). No baseline characteristic was significantly associated with the rate of decline in LVEF over time in mixed-effects models, although there was a trend toward steeper LVEF decline among patients with higher baseline serum creatinine and lower hemoglobin levels (p = 0.056 and p = 0.055 for interactions with time, respectively).

There were 50 deaths during follow-up; the 3-year mortality was 15.3%. Baseline LVEF was not associated with mortality. However, in models with time-updated LVEF, patients who developed LVEF <40% over time had subsequently 5-fold higher mortality compared with those who maintained a LVEF ≥40% throughout the follow-up (Figure 4). Patients who developed LVEF <40% had also 3-fold higher rate of death or HF-related hospitalization (Figure 4). These associations persisted in models adjusting for clinical characteristics (Table 2). The association of a new LVEF <40% with the composite endpoints of death or cardiovascular

Table 1
Patient characteristics of the main cohort (N = 322) in comparison to patients not included because of lack of echocardiographic follow-up (N = 123)

Characteristic	Echo Follow-up		
	Yes (N = 322)	No (N = 123)	p Value
Age (years)	72.8 (63.3, 81.9)	73.1 (62.2, 84.5)	0.548
Women	184 (57.1%)	73 (59.4%)	0.748
White	162 (50.3%)	65 (52.8%)	
Black	145 (45.0%)	54 (43.9%)	0.793
Other/mixed race	15 (4.7%)	4 (3.2%)	
Body mass index (kg/m^2)	31.5 (26.7, 37.5)	29.4 (24.6, 38.5)	0.259
Left ventricular ejection fraction (%)	55 (50, 60)	55 (50,60)	0.527
Systolic blood pressure (mm Hg)	130 (118, 146)	136 (119,150)	0.264
Diastolic blood pressure (mm Hg)	70 (60, 80)	70 (62,80)	0.404
Heart rate (beats/min)	72 (65, 82)	72 (64,85)	0.931
Smoker			0.617
Current	24 (7.5%)	12 (9.8%)	
Former	86 (26.7%)	29 (23.6%)	
New York Heart Association class			0.915
I−II	241 (74.8%)	94 (76.4%)	
III−IV	79 (24.5%)	28 (22.8%)	
Hypertension	296 (91.9%)	108 (87.8%)	0.200
Diabetes mellitus	147 (45.6%)	47 (38.2%)	0.166
Coronary artery disease	147 (45.6%)	47 (38.2%)	0.166
Coronary revascularization	126 (39.1%)	37 (30.1%)	0.080
Non-coronary cardiac surgery	40 (12.4%)	6 (4.9%)	0.033
Atrial fibrillation/flutter	144 (44.7%)	46 (37.4%)	0.166
Cerebrovascular disease	41 (12.7%)	21 (17.1%)	0.284
Peripheral vascular disease	32 (9.9%)	8 (6.5%)	0.354
Chronic lung disease	81 (25.2%)	30 (24.4%)	0.903
Sleep apnea	81 (25.2%)	24 (19.5%)	0.261
Depression	40 (12.4%)	26 (21.1%)	0.025
Dementia	6 (1.9%)	12 (9.8%)	<0.001
History of systemic cancer	38 (11.8%)	11 (8.9%)	0.498
Anemia*	167 (51.9%)	61 (50.0%)	0.643
Hemoglobin (g/dL)	12.1 (10.7, 13.2)	12.2 (11.2, 13.4)	0.334
Sodium (mEq/dL)	139 (137, 140)	139 (137, 140)	0.941
Potassium (mEq/dL)	4.1 (3.8, 4.5)	4.1 (3.9, 4.4)	0.880
Fasting glucose (mg/dl)	103 (90, 131)	106 (92.5, 134)	0.445
Blood urea nitrogen (mg/dl)	22 (15, 32)	20 (15.5, 26.5)	0.044
Creatinine (mg/dl)	1.20 (0.90, 1.52)	1.13 (0.91, 1.36)	0.108
Estimated glomerular filtration rate, (ml/min/1.73m^2)†	56 (41, 75)	60 (44, 76)	0.145
Total protein (g/dL)	7.0 (6.6, 7.4)	6.9 (6.5, 7.4)	0.883
Serum albumin (g/dl)	3.6 (3.3, 3.9)	3.7 (3.3, 3.9)	0.998
Total cholesterol (mg/dL)	151 (125, 178)	149 (118, 173)	0.887
Low-density lipoprotein cholesterol (mg/dL)	78 (58, 103)	77 (58, 107)	0.811
High-density lipoprotein cholesterol (mg/dL)	44 (36, 53)	40 (32, 54)	0.121
Triglycerides (mg/dL)	103 (70, 153)	99 (69, 174)	0.972
Therapy			
ACE inhibitor	116 (36.0%)	61 (50.0%)	0.010
Angiotensin receptor blocker	75 (23.3%)	25 (20.3%)	0.528
Beta blocker	259 (80.4%)	92 (74.8%)	0.196
Aldosterone receptor blocker	49 (15.2%)	17 (13.8%)	0.767
Calcium channel clocker	122 (37.9%)	34 (27.6%)	0.046
Digoxin	21 (6.5%)	10 (8.1%)	0.538
Nitrates	75 (23.3%)	16 (13.0%)	0.018
Diuretics	267 (82.9%)	97 (78.9%)	0.338
Pacemaker	49 (15.2%)	16 (13.0%)	0.653
Implantable cardioverter defibrillator	20 (6.2%)	6 (4.9%)	0.821

ACE = angiotensin-converting enzyme.
Values for continuous variables represent median (interquartile range); values for discrete variables represent N (%).
* Defined as hemoglobin < 13 g/dL in men and <12 g/dL in women.
† Calculated with the Modification of Diet in Renal Disease study equation.

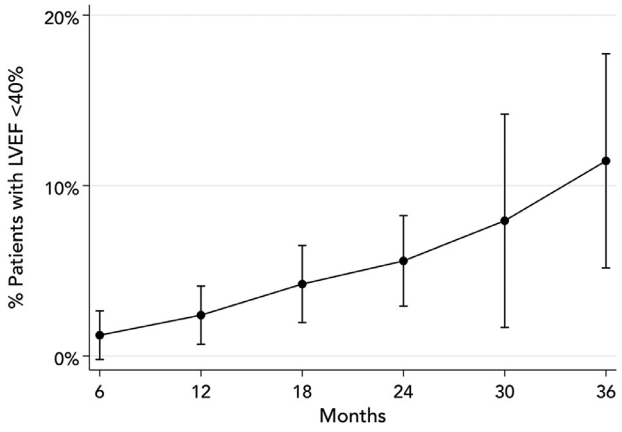

Figure 1. Incidence of left ventricular ejection fraction <40% over time. Bars represent 95% confidence interval. LVEF = left ventricular ejection fraction.

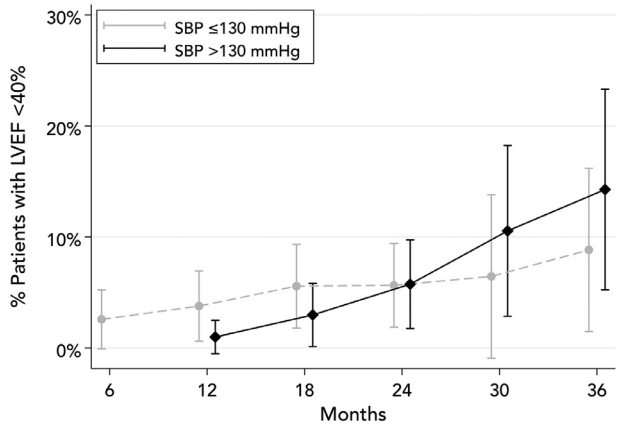

Figure 2. Incidence of left ventricular ejection fraction <40% according to systolic blood pressure at baseline. Bars represent 95% confidence interval. LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

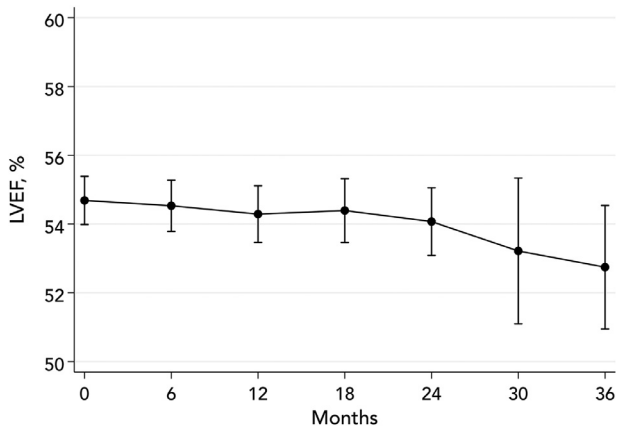

Figure 3. Evolution of left ventricular ejection fraction as a continuous variable over time. LVEF = left ventricular ejection fraction.

hospitalization and death or any hospitalization was weaker (Table 2, Supplemental Figure 1). The risks associated with a decrease in LVEF were similar across sex and race groups (data not shown).

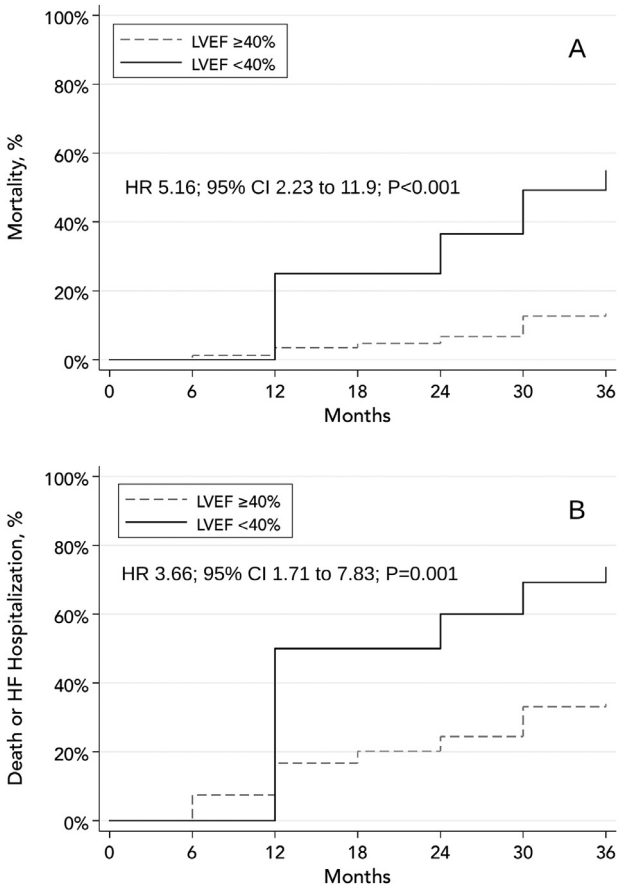

Figure 4. Cumulative incidence of *(A)* death and *(B)* death or hospitalization for heart failure after development of left ventricular ejection fraction <40%. Hazard ratio and confidence interval derived with crude Cox proportional hazards model. CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction.

In an analysis of interval hospitalizations with primary reasons related to acute coronary syndromes, diabetes complications, acute or worsening renal failure, or cancer (Supplemental Table 1), 16.7% of patients who developed reduced LVEF versus 12.8% of those who did not (p = 0.57) had any type of interval event during follow-up. Only 10% of patients with LVEF deterioration experienced a coronary event versus 3.8% of those without (p = 0.135). However, the number of events was small, and therefore these results should be interpreted with caution.

In the subset of patients with baseline LVEF ≥50% (N = 265), the association of new LVEF <50% with subsequent events and composite endpoints had similar direction and trends but the magnitude was weaker and not significant in adjusted models (Supplemental Table 2).

Discussion

In this study, 11.4% of ambulatory patients with HFpEF experienced a decline of systolic function, expressed as LVEF <40%, by 3 years. These patients had a 5-fold higher mortality subsequently, and increased incidence of death or HF-related hospitalization, compared with the patient population who maintained a LVEF ≥40%. These findings were

Table 2
Association of time-updated drop (to <40%) in left ventricular ejection fraction with subsequent events

Endpoint	Crude		Adjusted*	
	Hazard ratio (95%CI)	p Value	Hazard ratio (95%CI)	p Value
Death	5.16 (2.23−11.9)	<0.001	4.91 (2.00−12.0)	0.001
Death or hospitalization for heart failure	3.66 (1.71−7.83)	0.001	3.26 (1.51−7.04)	0.003
Death or cardiovascular hospitalization	2.36 (0.86−6.48)	0.095	2.16 (0.83−5.62)	0.114
Death or all-cause hospitalization	2.21 (0.63−7.76)	0.214	3.08 (0.91−10.4)	0.071

CI = confidence interval. revised discussion. Hospitalizations were classified based on primary admission diagnosis into cardiovascular and non-cardiovascular, with the former being further divided into HF-related and non-HF-related.

‡* Adjusted for age, gender, body mass index, New York Heart Association class, hypertension, diabetes, coronary artery disease, atrial fibrillation, anemia, depression, chronic lung disease, blood pressure, heart rate, renal function, electrolytes, albumin, lipids, medications, and devices.

consistent across race (African-American or Caucasian) and gender subgroups. The results were similar in direction when a LVEF ≥50% was used as cut-off for preserved systolic function, albeit power was limited for this analysis in our study. Among baseline risk factors, elevated systolic blood pressure was associated with a decline in LVEF.

A number of studies have reported a longitudinal downtrend of LVEF in patients with HFpEF.[6,10,11] In a study using multistate Markov modeling to estimate LVEF transition rates,[10] 11.0% of patients with initial LVEF >40% had a subsequent visit with reduced LVEF over a median of 4.1 years, a finding that is similar to our report. However, that study did not report mortality after LVEF transition.[10] The rate of LVEF decline was slower in our study compared with the Olmsted County data,[6] but baseline LVEF was higher by definition in that study (LVEF ≥50%). Similar data for patients with LVEF ≥50% have been reported by a Japanese registry, although competing mortality was high in that study.[12] In the same study, patients with midrange LVEF demonstrated a higher propensity for transition to reduced LVEF. This was confirmed by a report from Europe, where 24% of patients with midrange LVEF developed reduced LVEF in 1 year. Therefore, our data reflect transition rates of a HFpEF population at intermediate risk, as we included 57 patients with the newly proposed midrange LVEF definition in our study.

Two studies have linked development of reduced LVEF with worse outcomes in HFpEF. In the Olmsted County study, a decline in LVEF of 5% was associated with 7% higher mortality, but no data were provided for LVEF category transitions.[6] In the Japanese registry, transition to reduced LVEF after 1 year among patients with initial HFpEF was associated with 3-fold higher mortality in the next year compared with patients with persistent HFpEF.[12] In the same study, transition of midrange LVEF to reduced LVEF was associated with worse prognosis.[12] Findings had a similar direction in a European cohort.[13] Our study is the first to report the impact of transition from the HFpEF category (including midrange LVEF) to reduced LVEF on mortality and a hospitalization composite endpoint.

Of the baseline characteristics, only elevated systolic blood pressure had a significant association with the development of LVEF <40%. Hypertension has been identified as a key risk factor for HFpEF, with a diagnosis of hypertension preceding ∼90% of new cases,[14] a finding that was replicated in our study. Antihypertensive therapy reduces the mechanical work that is required to maintain cardiac output and thus overall minimizes concentric remodeling and myocardial oxygen demand.[15] Therefore, inadequate blood pressure control may contribute to deterioration of systolic function. We observed that baseline systolic blood pressure >130 mm Hg was associated with LVEF decline in our study, a finding that is consistent with the current recommendations to treat blood pressure to stricter targets (<130 mm Hg for systolic blood pressure) both in the general population [16] but also specifically in patients with HFpEF after addressing elements of volume overload with diuretics.[17]

In the Dallas Heart Study, progression to dilated physiology among asymptomatic adults (median age, 44 years) with baseline left ventricular hypertrophy was uncommon (2% in 7 years) in the absence of interval myocardial infarction.[18] Of note, interval coronary events have been shown to have a major effect on LVEF deterioration in patients with left ventricular hypertrophy.[19] In contrast, progression to systolic dysfunction in our study was relatively frequent, despite that only 10% of patients with deteriorated LVEF experienced an interval acute coronary event. Other interval events were not more frequent in this group either. A potential explanation for the higher rate of LVEF deterioration in our study is the presence of clinically manifest (Stage C) HF at baseline, whereas in the Dallas Heart Study the participants with left ventricular hypertrophy were younger participants with subclinical (Stage B) disease. Thus, our patients had limited cardiac reserves and therefore were probably more vulnerable to the effects of elevated blood pressure or other forms of myocardial injury.

From a clinical perspective, our findings stress the need for better phenotyping of patients with HFpEF. Routine surveillance for systolic dysfunction (e.g., with echocardiography) would be inefficient, as most patients with HFpEF will not develop LVEF deterioration. Therefore, following the current recommendations to perform repeat echocardiography in these patients only when clinically alerted seems prudent.[20] However, the higher propensity for deterioration of LVEF among patients with midrange LVEF,[12,13] in conjunction with strain echocardiography studies indicating that systolic dysfunction is present in a substantial proportion of patients with HFpEF,[4,5] point to subgroups of patients with HFpEF behaving like HFrEF. These patients may benefit from more intensive neurohormonal blockade and potentially closer clinical and imaging surveillance. Prospective studies with strain echocardiography to identify patients with HFpEF who might benefit from neurohormonal blockade could provide proof of principle. In any case, treating systolic blood pressure to stricter targets in

patients with HF, as currently recommended, seems to protect systolic function in patients with HFpEF.

Our study has some limitations. First, our study population comes from a single academic center and thus our findings may not be generalizable to the broader population of patients with HFpEF. Second, the frequency of echocardiograms was not consistent among patients, as these echocardiograms were clinically indicated and thus subject to indication bias. Although clinical characteristics did not differ drastically according to availability of serial echocardiographic data, there were some differences in the prevalence of comorbidities, such as, depression and dementia. Third, data on left ventricular mechanics were not available in our study and thus we could not provide more insights into the evolution of systolic function over time and into components of left ventricular mechanics. However, the strong association between LVEF decline and mortality implies that LVEF deterioration actually reflects systolic dysfunction and it is not merely a reflection of, such as, altered loading conditions. Fourth, we did not have adequate numbers to explore the new midrange LVEF definition as a separate category.[21] However, the results were directionally similar when a cutoff of 50% was used to define reduced LVEF. Finally, the absolute number of patients who developed reduced LVEF in our study was small. As a result, the confidence intervals for the corresponding estimates were wide. Therefore, our findings must be interpreted cautiously until larger studies can provide more definitive estimates.

In conclusion, a proportion of ambulatory patients with HFpEF will develop a decline in LVEF within 3 years and these patients have a worse prognosis regardless of race or gender. Systolic blood pressure >130 mm Hg was associated with a decline in LVEF, thus supporting the current recommendations for stricter targets (<130 mm Hg). Future studies will inform us whether a subset of patients presenting with HFpEF have elements of systolic dysfunction and will benefit from neurohormonal blockade similar to that reserved for patients with HFrEF.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.052.

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