JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 6, 2018

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure

Josep Lupón, MD, PhD,[a,b,c,d] Giovana Gavidia-Bovadilla, MSc,[e,f] Elena Ferrer, MD,[b] Marta de Antonio, MD, PhD,[a,b] Alexandre Perera-Lluna, PhD,[f,g,h] Jorge López-Ayerbe, MD,[b] Mar Domingo, MD, PhD,[a] Julio Núñez, MD, PhD,[d,i,j] Elisabet Zamora, MD, PhD,[a,b,c,d] Pedro Moliner, MD,[a,b] Patricia Díaz-Ruata, MSc,[f,g] Javier Santesmases, MD,[a] Antoni Bayés-Genís, MD, PhD[a,b,c,d]

ABSTRACT

BACKGROUND Long-term trajectories of left ventricular ejection fraction (LVEF) in heart failure (HF) are incompletely characterized.

OBJECTIVES This study sought to examine LVEF trajectories in HF with reduced LVEF (<40%) and mid-range LVEF (40% to 49%) and the prognostic impact of LVEF dynamic changes over 15-year follow-up.

METHODS In this prospective, consecutive, observational registry of real-life HF outpatients, the authors performed 2-dimensional echocardiography at baseline and on a structured schedule after 1 year and then every 2 years up to 15 years.

RESULTS The mean number of LVEF measurements in the 1,160 included patients was 3.6 ± 1.7. As a whole, Loess curves of long-term LVEF trajectories showed an inverted U shape with a marked rise in LVEF during the first year, maintained up to a decade, and a slow LVEF decline thereafter (p for trajectory <0.001). This pattern was more pronounced in HF of nonischemic origin and in women. Patients with new-onset HF (≤12 months) had a higher early increase in LVEF, whereas patients with ischemic HF showed a lower LVEF increase at 1 year; both groups had a relative plateau thereafter. Patients with HF with mid-range LVEF had less of an increase (3 ± 9%) than those with HF with reduced LVEF (9 ± 12%) during the first year (p < 0.001), but the groups overlapped after 15 years. Patients who died had lower final LVEF and worse LVEF dynamics in the immediately preceding period than survivors.

CONCLUSIONS LVEF trajectories vary in HF depending on a number of disease modifiers, but an inverted U-shaped pattern with lower LVEF at both ends of the distribution emerged. A declining LVEF in the preceding period was associated with higher mortality. (J Am Coll Cardiol 2018;72:591-601) © 2018 by the American College of Cardiology Foundation.

Heart failure (HF) is a multifaceted syndrome that results in a wide spectrum of symptoms, ranging from exercise intolerance to fluid overload and congestion, and is associated with cardiac functional and structural abnormalities (1). Symptoms, together with left ventricular ejection fraction (LVEF), are currently the basis for diagnosis and management in HF. Both have been pivotal in clinical trials over the past 3 decades, providing the evidence base criteria for management of HF with

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain; [b]Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain; [c]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [d]Centro de Investigatión Biomédica en Red (CIBER) Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain; [e]Department of e-Health, Eurecat, Technological Center of Catalonia, Barcelona, Spain; [f]Departament d'Enginyeria de Sistemes, Automàtica i Informàtica Industrial, Universitat Politècnica de Catalunya, Barcelona, Spain; [g]Networking Biomedical Research Centre in Bioengineering, Biomaterials, and Nanomedicine (CIBER-BBN), Madrid, Spain; [h]Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain; [i]Cardiology Department, Hospital Clínico Universitario, INCLIVA, València, Spain; and the [j]Department of Medicine, Universitat de València, València, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 2, 2018; accepted May 3, 2018.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.05.042

ABBREVIATIONS AND ACRONYMS

ESC = European Society of Cardiology

HF = heart failure

HFmrEF = heart failure with mid-range left ventricular ejection fraction

HFpEF = HF with preserved ejection fraction

HFrEF = heart failure with reduced left ventricular ejection fraction

LME = linear mixed-effects

Loess = locally weighted error sum of squares

LVEF = left ventricular ejection fraction

depressed systolic function. HF with depressed systolic function is currently divided into 2 categories according to the most recent guidelines of the European Society of Cardiology (ESC): HF with reduced LVEF (HFrEF) and HF with mid-range LVEF (HFmrEF) (2).

Advances in HF treatment, including drug therapy, devices, coronary revascularization, and valvular repair (3), have achieved an increase or even normalization of LVEF in a substantial number of patients, which is known to carry a better prognosis (4–6); however, longitudinal analysis of LVEF trajectories over time is incomplete. Preliminary reports have been variable in size and follow-up, mainly in selected patients with shorter follow-up (6–11). Furthermore, the impact of LVEF dynamic changes on survival over time is not entirely characterized. Accordingly, the aim of the present study was to prospectively assess LVEF trajectories and outcomes over the long term (up to 15 years) in a real-life cohort of patients with HF and depressed systolic function of diverse causes.

SEE PAGE 602

METHODS

STUDY POPULATION AND OUTCOMES. All consecutive ambulatory patients referred to a structured multidisciplinary HF clinic of a university hospital between August 2001 and December 2015, regardless of etiology, were considered for the study. During the 15-year period, clinical pathways and referral geographic area, covering ~850,000 inhabitants in the northern Barcelona Metro Area, remained stable. The criteria for clinical practice referral to the HF clinic were HF with at least 1 hospitalization, depressed systolic function, or both (12).

All patients were seen regularly during follow-up visits at the HF clinic according to their clinical needs and treated according to a unified protocol. Follow-up visits included a minimum of 1 visit with a nurse every 3 months and 1 visit with a physician (cardiologist, internist, or family physician) every 6 months (Online Figure 1), as well as optional visits with specialists in geriatrics, psychiatry, and rehabilitation (12). During the baseline visit, patients provided written consent for the use of their clinical data for research purposes.

The main inclusion criteria for the present study were having had at least 2 echocardiography measurements, one at baseline and the other during follow-up. Patients undergoing heart transplantation or cardiac resynchronization therapy after the second echocardiography study were censored at the time of the intervention.

The study was performed in compliance with the law protecting personal data, in accordance with the international guidelines on clinical investigation of the World Medical Association's Declaration of Helsinki.

ECHOCARDIOGRAM STUDIES. LVEF was scheduled to be assessed at baseline and at 1, 3, 5, 7, 9, 11, 13, and 15 years of follow-up (Online Figure 1) by 2-dimensional echocardiography by image expert cardiologists. LVEF was obtained from apical 2- and 4-chamber views and calculated with the Simpson method. All echocardiograms were revised for accuracy by expert staff.

STATISTICAL ANALYSIS. Categorical variables were expressed as absolute numbers and percentages. Continuous variables were expressed as the mean ± SD or median (quartile 1 to quartile 3) according to normal or non-normal distributions. Normal distribution was assessed with normal Q to Q plots. Loess (locally weighted error sum of squares) curves were plotted for the whole cohort and the pre-specified study subgroups. Loess regression is a nonparametric approach developed in 1988 (13). Loess curves are useful to observe trend or relationship on nonlinear data observed over time. Loess moves along data looking at chunks at a time, fitting a set of local regression lines computed on observed data (missing values are omitted) and connecting these lines to make a smooth line. Missingness because of loss to follow-up was assumed to be at random because there was no evidence that not attending to the scheduled visit had anything to do with LVEF. Locally weighted regression is based on a weight function that gives the greatest weight to observations that are closest to the focal observation. Statistical analyses of LVEF change over time were performed by linear mixed-effects (LME) modeling. LME takes into account the group-level structure in the data by simultaneous assessing effects within and across groups. LME models incorporate both fixed effects and random effects (14) and describe the relationship between a response and the covariates that have been observed along with the response (15). In this study, LME models were developed to evaluate and compare the effect of time over the LVEF change for pre-specified subgroups according to etiology of HF, duration of HF at baseline, LVEF ESC classification (HFrEF vs. HFmrEF), and sex. We hypothesized that there are important individual-level

TABLE 1 Demographic, Clinical, and Therapeutic Characteristics of Patients at Baseline and Treatment During Follow-up

		N
Age, yrs	64.9 ± 12.3	1,160
Male	887 (76.5)	1,160
White	1,153 (99.4)	1,160
Etiology		1,160
Ischemic heart disease	662 (57.1)	
Dilated cardiomyopathy	160 (13.8)	
Hypertensive	82 (7.1)	
Alcohol induced	68 (5.9)	
Drug induced	35 (3.0)	
Valvular	70 (6.0)	
Other	83 (7.2)	
HF duration, months	6 (1–40)	1,160
NYHA functional class		1,160
I	60 (5.2)	
II	817 (70.4)	
III	277 (23.9)	
IV	6 (0.5)	
LVEF, %	30.4 ± 8.4	1,160
LV end-diastolic diameter, mm	61.4 ± 8.3	1,043
LV end-systolic diameter, mm	49.3 ± 9.5	1,027
Diabetes mellitus	461 (40.0)	1,160
Hypertension	713 (61.5)	1,160
Anemia*	497 (43.0)	1,160
Renal insufficiency†	471 (41.0)	1,160
Atrial fibrillation/flutter	203 (17.5)	1,160
LBBB	155 (13.4)	1,160
Heart rate, beats/min	70.7 ± 14.6	1,160
Blood pressure, mm Hg	125.5 ± 21.7	1,160
BMI, kg/m^2	27.0 (24.3–30.3)	1,156
NTproBNP, ng/l	1,623 (709–3,709)	714
Treatments (baseline)		
ACE inhibitor or ARB	1,063 (91.6)	1,160
β-blocker	886 (76.4)	1,160
MRA	391 (33.7)	1,160
Loop diuretic agent	873 (75.3)	1,160
Digoxin	258 (22.2)	1,160
Ivabradine	72 (6.2)	1,160
Sacubitril/valsartan	0 (0.0)	1,160
CRT	0 (0.0)	1,160
ICD	74 (6.4)	1,160
Treatments (follow-up)		
ACE inhibitor or ARB	1,084 (93.4)	1,160
β-blocker	1,094 (91.6)	1,160
MRA	778 (67.1)	1,160
Loop diuretic agent	1,062 (91.6)	1,160
Digoxin	477 (41.1)	1,160
Ivabradine	235 (20.3)	1,160
Sacubitril/valsartan	44 (3.8)	1,160
CRT	68 (5.9)	1,160
ICD	171 (14.7)	1,160
Revascularization procedure	97 (8.4)	1,160

Values are mean ± SD, n (%), or median (interquartile range). *According to World Health Organization criteria (<13 g/dl in men and <12 g/dl in women). †Estimated glomerular filtration rate (CKD-EPI equation) <60 ml/min/1.73 m^2.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NTproBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

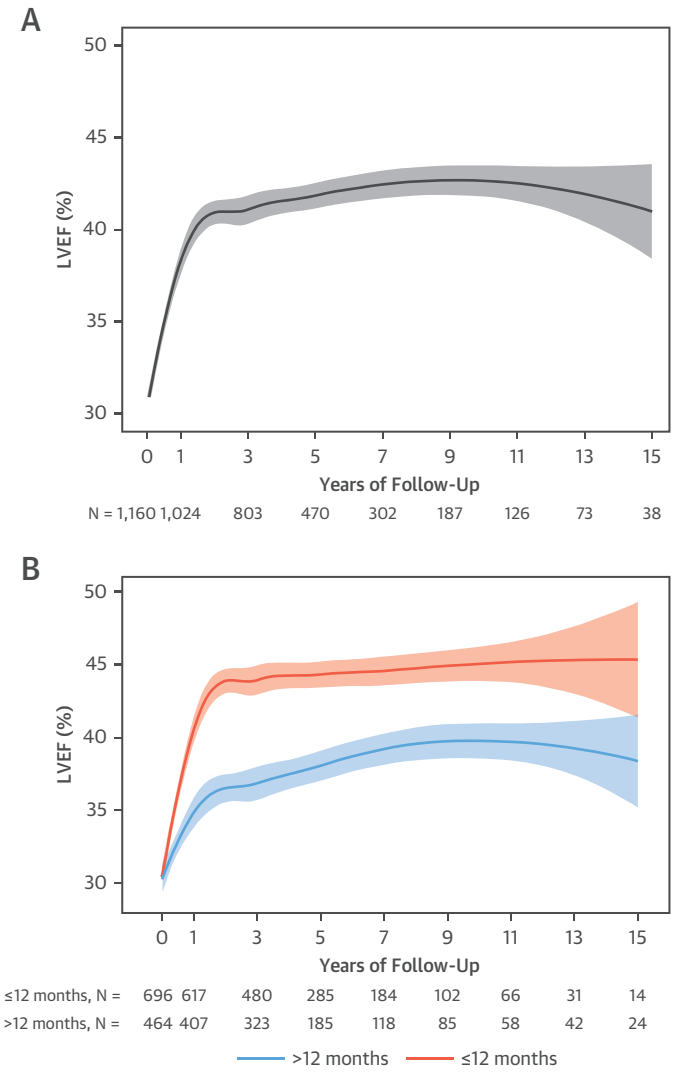
Continued in the next column

effects and that patients have similar rates of change over time. Thus, we fitted random intercepts LME models in which the measured value of LVEF was assumed to have a set of parameters fixed across individuals, including a specific random effect per each individual. Because the form of the Loess curves suggests at least a quadratic in time, all LME models included both the linear term *time* and the quadratic term *time^2* as fixed effects. By adding the quadratic term *time^2* to the models, we could evaluate whether the effect of time changed significantly as the time progressed. The Wald chi-square test was applied to evaluate how confident our estimates of the effect of time on LVEF values were. Comparisons of LVEF between groups were also performed at every time point of the study with paired Student's *t*-test. Comparisons between included and excluded patients and between alive and dead patients were performed with the Student's *t*-test, Mann-Whitney *U* test, or chi-square test, as appropriate. Statistical analyses were performed with SPSS 21 (SPSS, Chicago, Illinois) and R (A Language and Environment for Statistical Computing) by R Core Team (R Foundation for Statistical Computing, Vienna, Austria, 2017). For LME models, we used the nlme R package, version 3.1-131 by Pinheiro, Bates, DebRoy, Sarkar and R Core Team (2017). A 2-sided $p < 0.05$ was considered significant.

RESULTS

A total of 1,921 patients were admitted to the HF clinic from August 2001 to December 2015, 1,656 of whom had LVEF <50%. After exclusion criteria were applied, 1,160 had a minimum of 2 LVEF measurements and constituted the study population (Online Figure 2). **Table 1** shows clinical, biochemical, echocardiographic, and treatment characteristics of the studied cohort at baseline, as well as treatment during follow-up. The main etiology was ischemic heart disease (56%), followed by dilated cardiomyopathy (14%). Medical treatment was optimized during follow-up (**Table 1**). Online Table 1 compares patients included and not included (lack of a second echocardiogram) to address group bias. Although some

FIGURE 1 Loess Spline Curves of Long-Term LVEF Trajectories



(A) Total cohort; $p < 0.001$ for trajectory changes of left ventricular ejection fraction (LVEF). **(B)** Comparison between patients with heart failure duration ≤1 year **(orange)** versus >1 year **(blue)**. $p < 0.001$ for LVEF trajectory changes for both groups; $p < 0.001$ for comparison between groups. **Shaded regions** represent 95% confidence interval.

differences were found, the variables primarily associated with LVEF dynamics, such as sex, etiology, baseline LVEF, and HF duration, showed no statistical differences.

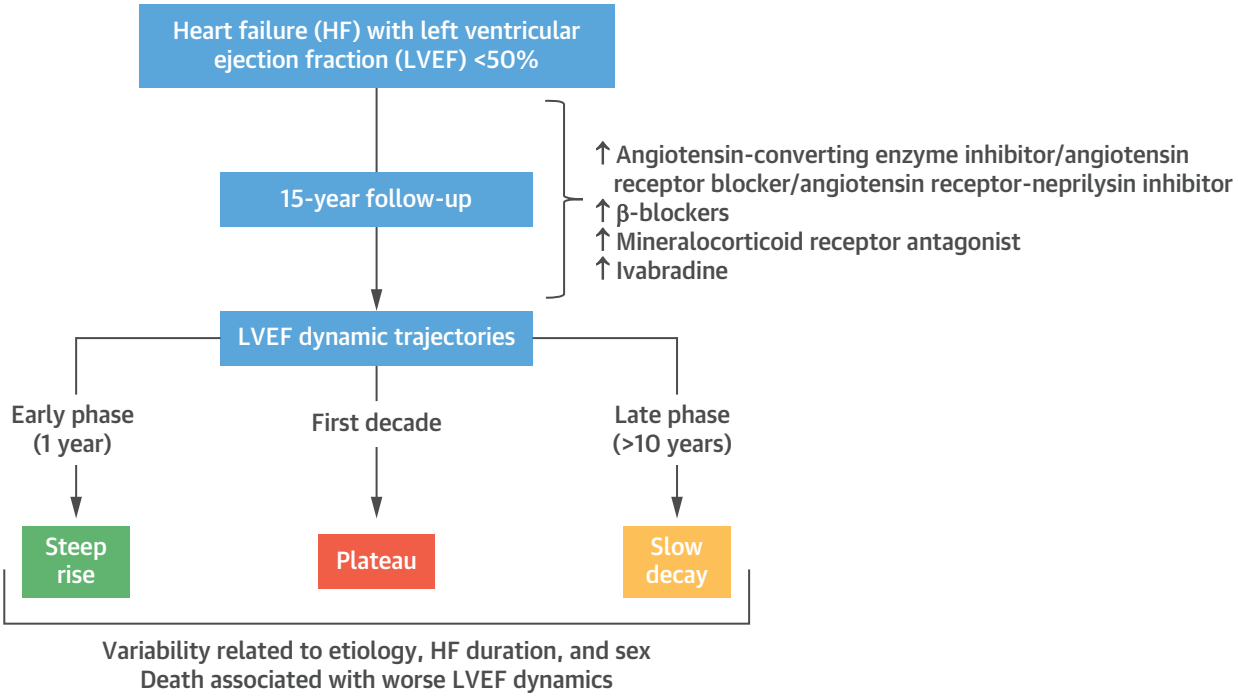
A total of 4,183 echocardiograms were performed during the study period. The prospective echocardiography schedule and the distribution of echocardiograms performed per patient (mean 3.6 ± 1.7, ranging from 2 in 398 patients to 9 in 16 patients) are shown in Online Figures 1 and 3, respectively. Survival curves and causes of death are shown in Online Figure 4 and Online Table 2, respectively. Mean LVEF values were 30 ± 8% (n = 1,160), 38 ± 12% (n = 1,024), 41 ± 13% (n = 803), 41 ± 12% (n = 471), 43 ± 12% (n = 302), 43 ± 12% (n = 187), 42 ± 12% (n = 126), 41 ± 10% (n = 73), and 42 ± 9% (n = 38) at baseline and 1, 3, 5, 7, 9, 11, 13, and 15 years, respectively. LVEF dynamic trajectories of the entire cohort at every time point are illustrated in **Figure 1A**. Paired data comparisons showed statistical differences between baseline and 1 year ($p < 0.001$), between 1 and 3 years ($p < 0.001$), and between 5 and 7 years ($p = 0.002$) (Online Table 3). As a whole, Loess splines of long-term LVEF trajectories showed an inverted U shape, with a marked rise in LVEF during the first year, maintained up to a decade, and a slow LVEF decline thereafter (p for trajectory <0.001) (**Central Illustration**). A more pronounced increase in LVEF during the first year was observed in new-onset HF (≤12 months) than in patients with longer HF duration at the baseline visit, followed by a plateau (**Figure 1B**) ($p < 0.001$ for both trajectories; $p < 0.001$ between groups).

Figure 2 shows LVEF trajectories relative to HF etiology. Ischemic HF patients showed a moderate LVEF increase at 1 year, with a relative plateau thereafter. Nonischemic HF patients showed a more pronounced bump at 1 year and a more prolonged increase during follow-up than those with ischemic HF (~7 to 10 LVEF points; $p < 0.001$ for both trajectories; $p < 0.001$ between groups) (**Figure 2A**). The greatest LVEF increase was observed in hypertensive HF (**Figure 2B**). Among nonischemic etiologies, the LVEF increase tended to be more limited in time (3 years) in toxic (chemotherapy) and valvular HF, whereas it extended to a decade in dilated cardiomyopathy and hypertensive HF and declined thereafter. Alcohol-induced cardiomyopathy as an etiology was associated with full recovery in the long-term ($p < 0.001$ for all trajectories).

Relative to ESC HF classification, patients with HFrEF experienced a steep rise the first year (9 ± 12%), with a slight upward trend during follow-up. By contrast, patients with HFmrEF showed a poorer LVEF increase (3 ± 9%) during the first year ($p < 0.001$ vs. HFrEF) and thereafter showed a downward trend. Hypertensive etiology (10.7% vs. 6.3%, $p = 0.03$) was significantly more frequent in HFmrEF, whereas alcohol toxicity tended to be more frequent in HFrEF (3.2% vs. 6.4%, $p = 0.09$).

Remarkably, at 15 years, HFmrEF was associated with slightly lower LVEF than HFrEF ($p = 0.98$; $p < 0.001$ for both trajectories; $p < 0.001$ between groups) (**Figure 3A**). The evolution of HFrEF showed that 56% of patients did not move out of the HFrEF

CENTRAL ILLUSTRATION **Left Ventricular Ejection Fraction Trajectories and Dynamics: 15 Years**



Lupón, J. et al. J Am Coll Cardiol. 2018;72(6):591-601.

Long-term left ventricular ejection fraction (LVEF) trajectories of the whole study cohort showed a marked increase during the first year, maintained up to a decade, with a slow LVEF decline thereafter. The early improvement was related to etiology (higher in nonischemic patients), heart failure (HF) duration (higher in HF of <12 months' duration), and sex (higher in women). LVEF dynamics are related to outcome: patients who died had worse dynamics in the immediately preceding study period than patients who remained alive (less initial improvement and greater declines afterward).

category, whereas 21% and 23% moved to the HFmrEF and HF with preserved ejection fraction (HFpEF) categories, respectively. By contrast, patients who had HFmrEF at baseline were fairly equally distributed across HFrEF (25%), HFmrEF (39%), and HFpEF (36%) at the end of follow-up (**Figure 3B**).

Women demonstrated higher LVEF than men both at baseline ($p < 0.001$) and up to 9 years later ($p = 0.001$) (**Figure 4**). In addition, LVEF recovery was significantly higher in women than in men ($p = 0.02$) during the first year, without significant differences thereafter. After 9 years of follow-up, women tended to show a decline and had values that were practically equal to those of men at 15 years ($p = 0.54$) ($p < 0.001$ for both trajectories; $p < 0.004$ between sexes).

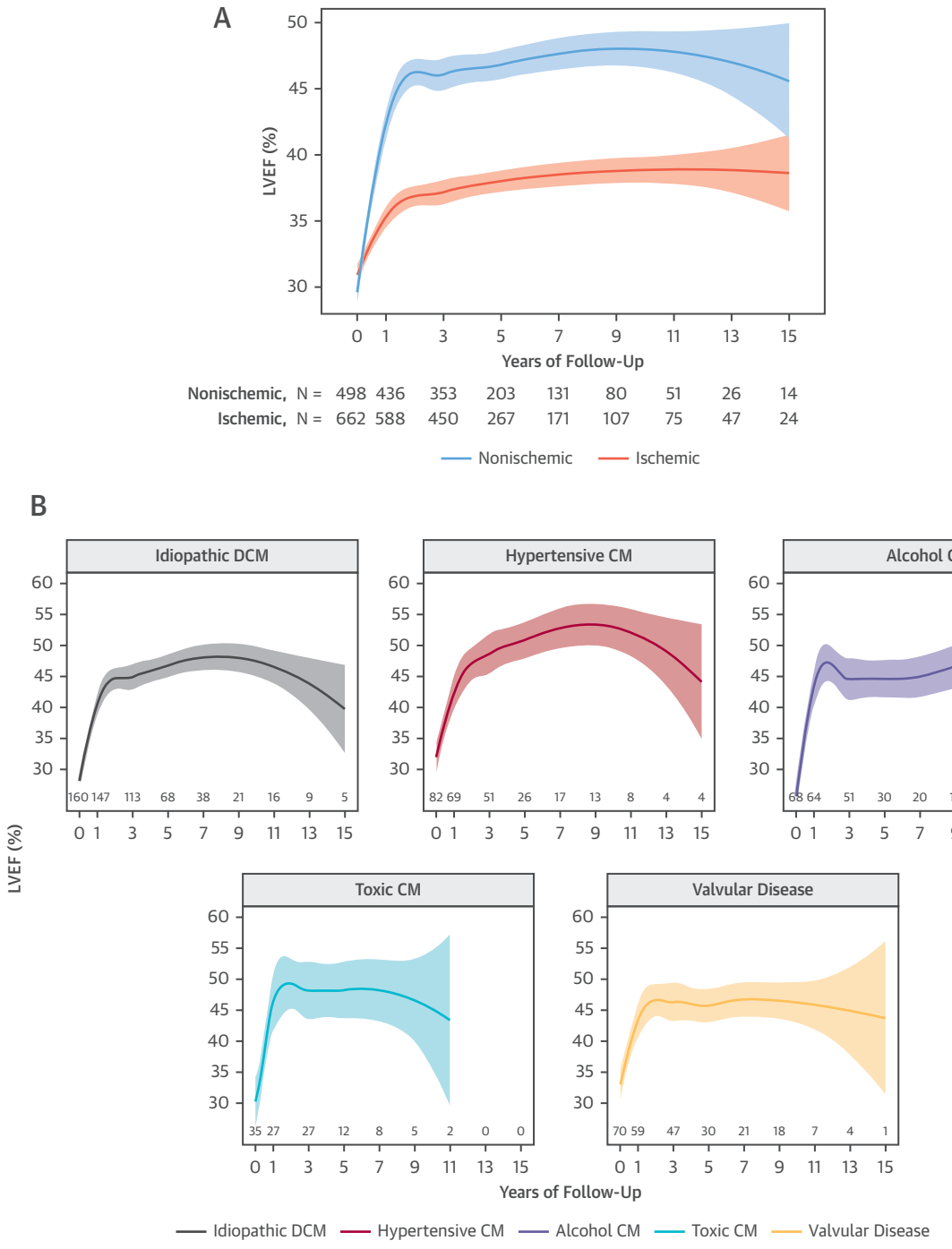
Online Figure 5 shows LVEF trajectories relative to HF hospitalization in the precedent year. A significant difference was found ($p < 0.001$), with greater early improvement in patients with previous hospitalization and a pronounced inverted-U shape during follow-up. Of note, among hospitalized patients, the majority were patients with HF of short duration (<1 year; $p < 0.001$) and mainly HFrEF (88%; $p < 0.001$).

Remarkably, during each study period, patients who died had lower previous LVEF than survivors (**Figure 5A**) and had worse LVEF dynamics in the immediately preceding study period (changes between the 2 previous LVEF assessments) during most of the follow-up (**Figure 5B**). Online Figure 6 shows Loess curves for LVEF trajectories of surviving patients at 15 years, the entire cohort, and decedents during follow-up.

DISCUSSION

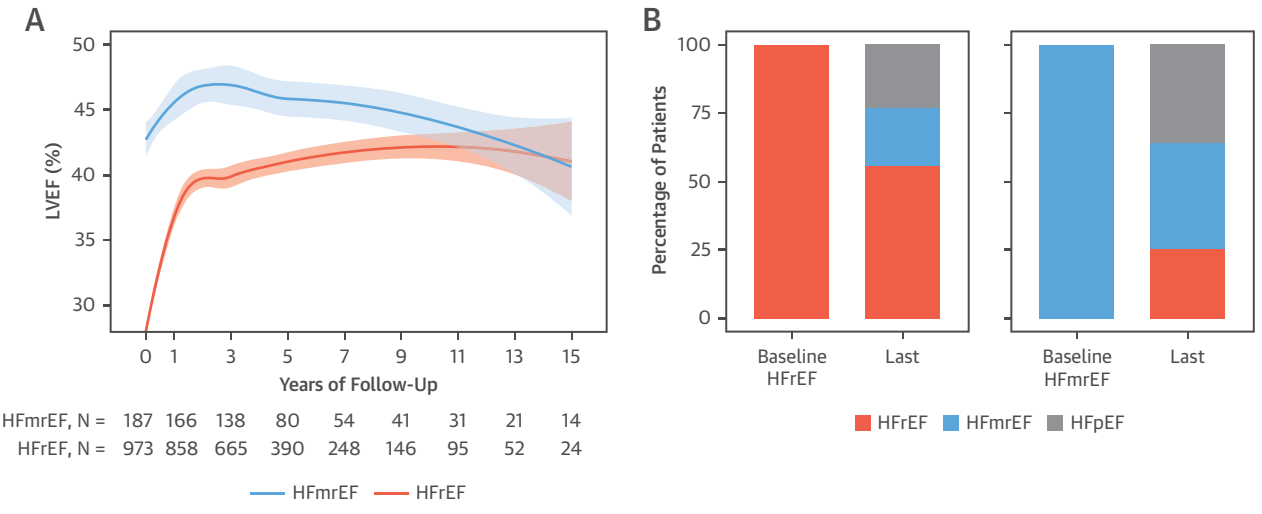
The present study is notable for its prospective assessment of LVEF trajectories in a consecutive real-life cohort of HF patients with depressed systolic function of diverse etiologies managed according to a structured HF clinic and echocardiographic schedule for 15 years. Remarkably, long-term HF mortality

FIGURE 2 **Loess Spline Curves of Long-Term LVEF Trajectories Based on Etiology**



(A) Ischemic **(orange)** versus nonischemic **(blue)** etiology of heart failure. $p < 0.001$ for left ventricular ejection fraction (LVEF) trajectory changes for both groups; $p < 0.001$ for comparison between groups. **(B)** Different nonischemic etiologies: **(top left)** dilated cardiomyopathy (DCM); **(top middle)** hypertensive cardiomyopathy; **(top right)** alcohol-induced; **(bottom left)** drug-induced; **(bottom right)** valvular disease. $p < 0.001$ for LVEF trajectory changes for all etiologies. Taking DCM as the reference, there were no statistically significant differences with the other etiologies, except for valvular disease, in the linear component of the trajectory ($p < 0.05$). **Shaded regions** represent 95% confidence interval. CM = cardiomyopathy.

FIGURE 3 LVEF Evolution According to European Society Cardiology Classification: HFrEF Versus HFmrEF

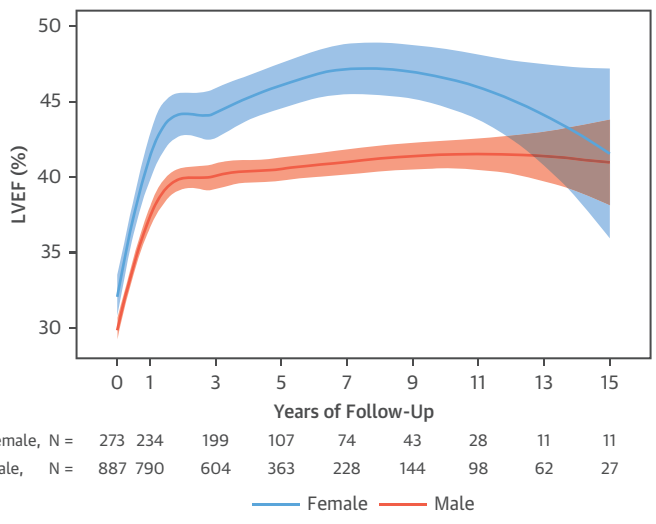


(A) Loess spline curves of long-term left ventricular ejection fraction (LVEF) trajectories. **Orange** indicates heart failure with reduced ejection fraction (HFrEF); **blue** indicates heart failure with mid-range ejection fraction (HFmrEF). $p < 0.001$ for LVEF trajectory changes for both groups; $p < 0.001$ for comparison between groups. **Shaded regions** represent 95% confidence interval. **(B)** Distribution of patients into HFrEF and HFmrEF classes at baseline and at the last observation for every patient. **(Left)** HFrEF patients at baseline; **(right)** HFmrEF patients at baseline. HFpEF = heart failure with preserved ejection fraction.

remains too high, with a 15-year mortality of 72%, yet the majority of patients alive were adequately studied. The 2 main relevant findings are as follows. First, LVEF trajectories are highly variable depending on etiology, HF duration at baseline visit, ESC classification, and sex but as a whole show a significant improvement at 1 year, with an LVEF rise up to a decade and a slow LVEF decline thereafter (**Central Illustration**). Second, a declining LVEF in the preceding period is associated with higher mortality. Each of these aspects is discussed below.

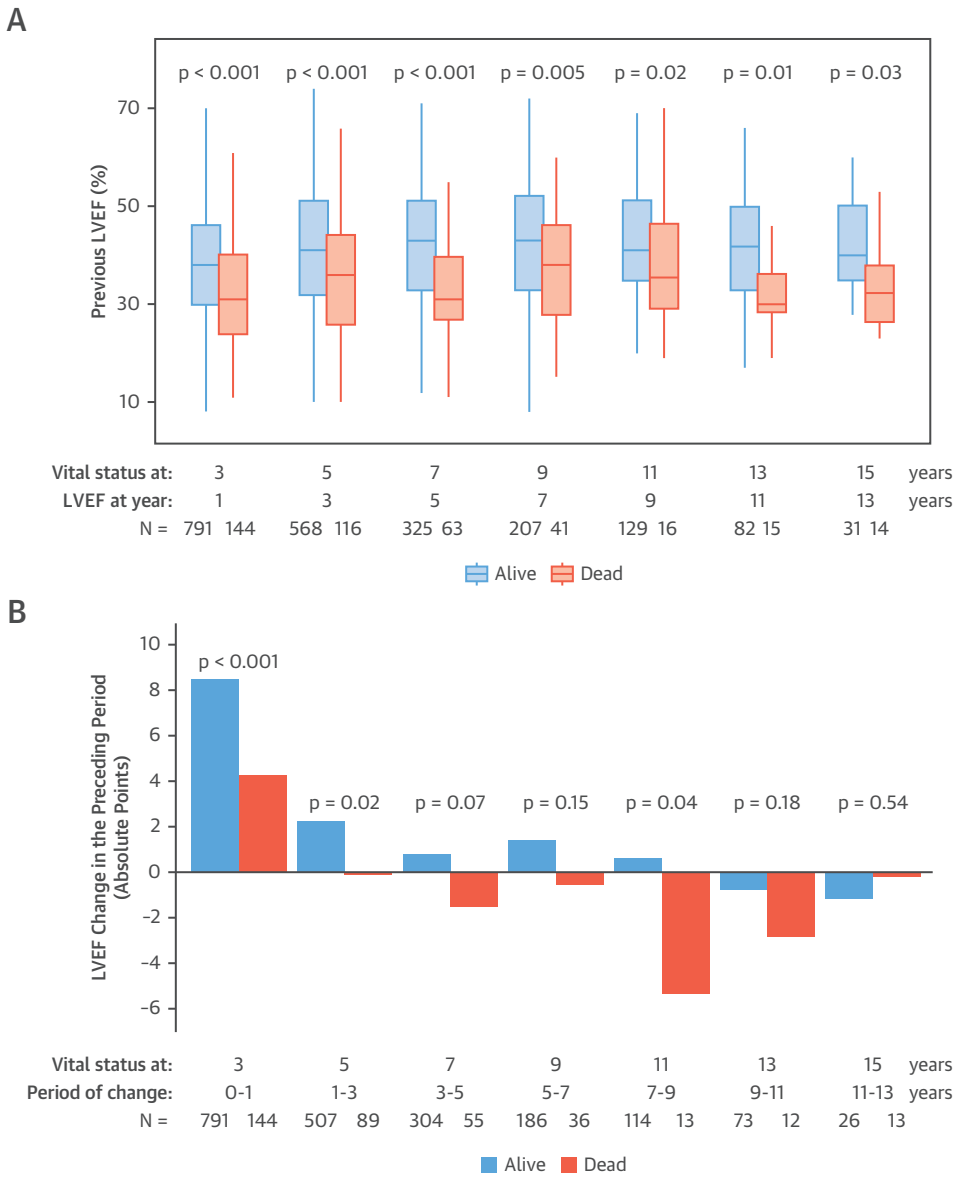
Most studies of HF with depressed systolic function, including clinical trials and observational studies, report only a single LVEF measurement, generally obtained at baseline. Nevertheless, HF includes multiple diverging patient-oriented phenotypes, resulting in a wide spectrum of time-dependent LVEF trajectories. Dunlay et al. (9) were among the first to report an LVEF increase of 6.9% over 5 years in a retrospective study begun in 1984 (before the first consensus trial was even published), which is far from the benefit achieved with current therapies. The transient nature of LVEF recovery has been described previously. Cioffi et al. (7), in a small prospective study, observed that LVEF normalization was subsequently lost in 55% of patients in the subsequent 2 years. De Groote et al. (8) reported that 25% of patients with LVEF recovery after β-blocker treatment experienced LVEF decline over time and that these patients were at higher risk for cardiovascular mortality. Finally, in a cohort of patients with dilated cardiomyopathy, Merlo et al. (10) reported a 37% LVEF deterioration over time among those who

FIGURE 4 Loess Spline Curves of Long-Term LVEF Trajectories Based on Sex



Men **(orange)** versus women **(blue)**. $p < 0.001$ for left ventricular ejection fraction (LVEF) trajectory changes for both sexes. $p < 0.004$ for comparison between sexes. **Shaded regions** represent 95% confidence interval.

FIGURE 5 LVEF and Survival



(A) LVEF in the last echocardiogram before the analyzed study period vital status. **Orange** indicates those patients who died in the subsequent study period, and **blue** indicates those who survived for the entire subsequent period. The **central box** represents the values from the lower to the upper quartile; the **middle line** represents the median; and the **whiskers** extend from the minimum to the maximum value, excluding outside and far out values, which are not displayed. **(B)** Changes between the last 2 echocardiograms before the analyzed study period vital status. **Orange** indicates those patients who died in the subsequent study period, and **blue** indicates those who survived for the entire subsequent period.

experienced an initial LVEF rise. Our findings confirm these earlier data, but in a large cohort prospectively followed up over 15 years. We observed a LVEF increase up to a decade that thereafter began a slow decline. This U-shaped curve showed a variable time-dependent peak among different HF etiologies.

A remarkable finding of the current study is the striking inverted U-shaped LVEF trajectory for patients with HF of nonischemic etiology. We maintained neurohormonal blockade treatment in all patients irrespective of LVEF improvement, but continuing treatment in patients with significant

LVEF improvement remains controversial. Our data support that LVEF improvement in most patients represents myocardial remission rather than true myocardial recovery indicative of myocardial cure, and the decision to discontinue maintenance HF therapy, namely, ß-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists, requires careful consideration (16). A different pattern was observed for alcohol-related HF, which showed a continuous increase in LVEF to full recovery, thus suggesting that in the absence of alcohol consumption, discontinuation of treatment could be an option.

Relative to the new HF classification of the ESC, we observed that patients with baseline HFrEF experienced a more pronounced LVEF increase than those with HFmrEF. HFrEF patients had worse LVEF at ≤7 years, but survivors in both HF categories progressively overlapped, and those with HFmrEF even tended to have worse numbers than those with HFrEF at 15 years. Whether HFmrEF is truly a distinct pathophysiological entity or rather represents a transitional phenotype is the subject of debate. In many instances, HFmrEF might be a transition phenotype of patients with HFrEF who are recovering (6,17). Indeed, in a cohort of patients with HF from Olmsted County, Minnesota, when the change in LVEF over time was quantified, LVEF increased by ~7% over 5 years in the HFrEF group (9). Our long-term data support the characterization of HFmrEF as just a snapshot on the way toward recovering or declining left ventricular systolic function rather than as a stable phenotype (18). Indeed, as shown in **Figure 3**, only slightly more than one-third of patients initially classified as having HFmrEF remained in that category during the full-term follow-up, whereas one-third evolved to HFpEF and 25% were categorized as having HFrEF. How to treat these patients is as yet unknown. At present, patients with HFmrEF receive inconsistent treatment, with some clinicians using HFrEF therapy (as we do) and others awaiting more evidence and guideline recommendations.

Sex differences were also observed, including better LVEF dynamics among women, who had higher baseline and subsequent LVEF measurements up to 9 years. The exact mechanism underlying these differences is unclear, but sex-related differences in cardiac remodeling and the protective effects of estrogen against apoptosis could be among the explanations (19).

The potential of a "survival effect" in the reported Loess curves through follow-up should not be underestimated. In point of fact, in the present study, we observed that patients who died had lower final LVEF values and worse LVEF dynamics in the preceding study period. This has important clinical implications, and further research is needed to understand it better. Whether the beneficial effects of ß-blockers and angiotensin-affecting drugs in reverse remodeling are partially lost in the long-term because of a certain degree of drug resistance remains unclear. The long-term effect of sacubitril/valsartan eventually could shed some light on this issue. Nevertheless, clear guidance is lacking on what to do for patients who experience a decline in LVEF over time despite optimal medical treatment. Remarkably, even taking into account the so-called survival effect, very long-term survival was accompanied by a progressive LVEF decay, which varied in intensity depending on the discussed clinical covariates.

STUDY LIMITATIONS. LVEF was assessed by transthoracic echocardiography in routine clinical care. However, in the current registry, all echocardiograms were scheduled prospectively and at pre-specified intervals, not at the discretion of the patient's physician, and were not retrospectively analyzed. We acknowledge that the intraobserver and interobserver variability of echocardiography-derived LVEF is ~5%; however, taking into account the large number of studies performed, we can assume that such variability was randomly distributed during follow-up. Furthermore, contrast echocardiography might be superior in the evaluation of left ventricular remodeling parameters; however, it is infrequently used in clinical practice, usually only in selected patients. Three-dimensional echocardiography and cardiac magnetic resonance imaging would evaluate left ventricular function and volumes more precisely, but they are not broadly used in clinical practice. As in all published studies of changes in left ventricular function during follow-up, our analyses were performed in "completers," that is, patients with both baseline and at least 1-year echocardiography data available for analysis. We cannot fully exclude some bias in Loess spline curves due to dropout, because we could not statistically distinguish between autonomous time trends and pseudo-upward trends because of successive dropout of fatalities with lower initial LVEF values. Missingness because of loss to follow-up was assumed to be at random. Furthermore, Loess spline curve estimations at the end of follow-up are less robust because of the limited number of patients. At present, there is a lack of evidence-based data on the best treatment for

HFmrEF patients, but in our HF clinic, we managed them as HFrEF. Mineralocorticoid receptor antagonists, ivabradine, and sacubitril/valsartan have been included in the therapeutic portfolio when they were included in international guidelines. How the introduction of such therapies influenced long-term LVEF is incompletely characterized.

The study cohort was a general HF population treated at a specific multidisciplinary HF clinic in a tertiary care hospital, with most patients referred from the cardiology department; thus, there was a predominance of relatively young men with HF of ischemic etiology, and an almost exclusively white population, so the results may not be able to be fully extrapolated to other populations. Of note, a common protocol of treatment was applied to all patients, thus limiting possible bias introduced by different management strategies or treatment protocols. However, dose change/discontinuation and drug reintroduction occur often during follow-up, and it is not possible to analyze the influence of all these changes in LVEF evolution. The reduced number of patients revascularized over the 15-year follow-up prevented us from knowing the actual impact of revascularization on LVEF dynamics above and beyond guideline-directed medical therapy.

CONCLUSIONS

Each patient with cardiac dysfunction will follow an individual trajectory within a wide spectrum of LVEF, depending on the number of disease modifiers. LVEF trajectories vary depending on HF etiology, HF duration, ESC classification, and sex. In this study, nonischemic HF patients showed a pattern of temporal myocardial remission without full recovery (except most alcohol-derived cases). Patients with ischemic HF showed an LVEF increase mainly during the first year and then remained stable. A declining LVEF in the preceding period was associated with higher mortality.

ACKNOWLEDGMENTS The authors thank Beatriz González, Roser Cabanes, Margarita Rodríguez, Carmen Rivas, Violeta Díaz, Nuria Benito, and Alba Ros, nurses in the HF unit, for data collection and their invaluable work in the unit. The authors also thank physicians Nuria Vallejo, Francisco Gual, Albert Teis, and Gladys Juncà from the echocardiography laboratory of the cardiology service for their valuable daily work. The authors also acknowledge Redes Temáticas de Investigación Cooperativa en Salud (RETICS) and Red Cardiovascular (RD12/0042/0047).

ADDRESS FOR CORRESPONDENCE: Dr. Antoni Bayés-Genís, Heart Institute, Department of Medicine, Universitat Autònoma de Barcelona, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet s/n 08916 Badalona, Spain. E-mail: abayesgenis@gmail.com. Twitter: @hgermanstrias, @UABBarcelona.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The trajectories of left ventricular ejection fraction (LVEF) as it changes over time vary in patients with heart failure (HF) depending on several disease modifiers (e.g., HF etiology and duration, patient sex), but an inverted U-shaped pattern with lower LVEF early and late in the course typically occurs. A declining LVEF in the preceding period is associated with higher mortality.

TRANSLATIONAL OUTLOOK: Contemporary medical treatment of HF with depressed ejection fraction is associated with an early rise in LVEF, followed by a plateau for about a decade and a slow decline thereafter. Treatments that extend myocardial recovery for a longer period of time could reduce mortality.

REFERENCES

1. 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.

2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

3. Hellawell JL, Margulies KB. Myocardial reverse remodeling. Cardiovasc Ther 2012;30:172–81.

4. Basuray A, French B, Ky B, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation 2014;129:2380–7.

5. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016;1:510–8.

6. Lupón J, Díez-López C, de Antonio M, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. Eur J Heart Fail 2017;19:1615–23.

7. Cioffi G, Stefenelli C, Tarantini L, Opasich C. Chronic left ventricular failure in the community: prevalence, prognosis, and predictors of the complete clinical recovery with return of cardiac size and function to normal in patients

undergoing optimal therapy. J Card Fail 2004; 10:250–7.

8. de Groote P, Fertin M, Duva Pentiah A, Goéminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. Circ Heart Fail 2014;7:434–9.

9. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012; 5:720–6.

10. Merlo M, Stolfo D, Anzini M, et al. Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? J Am Heart Assoc 2015;4:e001504.

11. Green P, Anshelevich M, Talreja A, et al. Long-term effects of carvedilol or metoprolol on left ventricular function in ischemic and nonischemic cardiomyopathy. Am J Cardiol 2005;95:1114–6.

12. Zamora E, Lupón J, Vila J, et al. Estimated glomerular filtration rate and prognosis in heart failure: value of the Modification of Diet in Renal Disease Study-4, Chronic Kidney Disease Epidemiology Collaboration, and Cockcroft-Gault formulas. J Am Coll Cardiol 2012;59:1709–15.

13. Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. J Am Stat Assoc 1988;83: 596–610.

14. Bates DM. lme4: mixed-effects modeling with R. Springer, 2010. Available at: http://lme4.r-forge.r-project.org/. Accessed January 2016.

15. Carey VJ, Wang Y-G. Book review: Mixed-Effects Models in S and S-Plus. J Am Stat Assoc 2001;96:1135.

16. Basuray A, Fang JC. Management of patients with recovered systolic function. Progress Cardiovasc Dis 2016;58:434–43.

17. Tsuji K, Sakata Y, Nochioka K, et al., on behalf of the CHART-2 Investigators. Characterization of heart failure patients with mid-range left ventricular ejection fraction: a report from the CHART-2 Study. Eur J Heart Fail 2017;19: 1258–69.

18. Bayés-Genís A, Nuñez-Villota J, Lupón J. Heart failure with mid-range ejection fraction: a transition phenotype? Eur J Heart Fail 2017;19: 1635–7.

19. Piro M, Della Bona R, Abbate A, Biasucci LM, Crea F. Sex-related differences in myocardial remodeling. J Am Coll Cardiol 2010;55:1057–65.

KEY WORDS ejection fraction, etiology, heart failure, long-term follow-up, ventricular function

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