Left Ventricular Ejection Fraction Dynamic Trajectories in Heart Failure:  
A 15-year Prospective Longitudinal Study

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ABSTRACT

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

**Objective:** To examine LVEF trajectories in HF with reduced LVEF (<40%; HFrEF) and mid-range LVEF (40-49%; HFmrEF) 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, we performed two-dimensional echocardiography at baseline and on a structured schedule after one year and then every two years up to 15 years.

**Results:** The mean number of LVEF measurements in the 1160 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 non-ischemic etiology and women. New-onset HF (≤12 months) had a higher LVEF early increase whereas ischemic HF patients showed a lower LVEF increase at one year, both groups with a relative plateau thereafter. LVEF with HFmrEF increased less (+3%±9) than with HFrEF (+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 immediate preceding period than survivors.

**Conclusions:** LVEF trajectories vary in HF depending on a number of disease modifiers, but an inverted U-shape pattern with lower LVEF at both ends of the distribution emerged. A declining LVEF in the preceding period was associated with higher mortality.
CONDENSED ABSTRACT

Long-term trajectories of left ventricular ejection fraction (LVEF) in heart failure (HF) are incompletely characterized. We prospectively examined LVEF trajectories in 1160 patients with LVEF <50% and the prognostic impact of LVEF dynamic changes over 15-year follow-up. LVEF trajectories vary in HF depending on a number of disease modifiers (etiology, HF duration, sex), but an inverted U-shape pattern with lower LVEF at both ends of the distribution emerged. Remarkably, a declining LVEF in the preceding period was associated with higher mortality. Patients who died had lower final LVEF and worse LVEF dynamics in the immediate preceding period than survivors.

**Keywords:** heart failure, ejection fraction, ventricular function, etiology, long-term follow-up
ABBREVIATIONS

HF = Heart failure
LVEF = left ventricular ejection fraction
ESC European Society of Cardiology
HFrEF Heart failure with reduced left ventricular ejection fraction
HFmrEF Heart failure with mid-range left ventricular ejection fraction
LME Linear Mixed-Effects
INTRODUCTION

Heart failure (HF) is a multifaceted syndrome resulting in a wide spectrum of symptoms, ranging from exercise intolerance to fluid overload and congestion, 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 last three decades, providing the evidence base criteria for management of HF with depressed systolic function. HF with depressed systolic function is currently divided into two 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 also 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 etiologies.

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 geographical area, covering ~850,000 inhabitants in the northern Barcelona Metro Area, have remained stable. The criteria for clinical practice referral to the HF clinic were HF with at least one hospitalization and/or depressed systolic function.12

All patients were regularly seen 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 one visit with a nurse every 3 months and one visit with a physician (cardiologist, internist, or family physician) every 6 months (Supplementary 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 two echocardiography measurements, one at baseline and the other during follow-up. Patients undergoing heart transplantation or cardiac resynchronization therapy after the second echocardiography 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 prospectively scheduled at baseline and at 1, 3, 5, 7, 9, 11, 13, and 15 years of follow-up (Supplementary Figure 1) by two-dimensional echocardiography by image expert cardiologists. LVEF was obtained from apical 2- and 4-chamber views and calculated using the Simpson’s 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 (standard deviation [SD]) or median (quartile Q1 to Q3) 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 non-parametric approach developed in 1988. Loess curves are useful to observe trend or relationship on non-linear data observed over time. Loess moves along data looking at chunks at a time, fitting a set of local regression lines that connect to make a smooth line. Locally weighted regression is based on a weight function, which gives the greatest weight to observations that closest to the focal observation. Statistical analyses of LVEF change along the 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 and describe the relationship between a response and covariates that have been observed along with the response. 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 European Society of Cardiology classification (HFrEF vs HFmrEF) and gender. We hypothesize that there are important individual-level effects and believe that patients have similar rates of change over time. Thus, we fitted “Random intercepts LME models”, where the measured value of LVEF is assumed to have a set of parameters fixed across individuals, but there is 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 time ‘time^2’. By adding the quadratic term ‘time^2’ to the models we evaluate whether the
effect of time changes significantly as the time progresses. The Wald Chi-square test was applied to evaluate how confident are our estimates of the effect of time on LVEF values. Comparisons on LVEF between groups were also performed at every time-point of the study using paired t-test. Comparisons between included and excluded patients and between alive and dead patients were performed using Student t-test, Mann-Whitney U test, or chi-squared test, as appropriate. Statistical analyses were performed using SPSS 21 (SPSS Inc., 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 two-sided P \(<0.05\) was considered significant.

RESULTS

A total of 1921 patients were admitted to the HF clinic from August 2001 to December 2015, and 1656 of them had LVEF <50%. After exclusion criteria were applied, 1160 had a minimum of two LVEF measurements and comprised the study population (Supplementary Figure 2). Table 1 shows clinical, biochemical, echocardiographic, and treatment characteristics of the studied cohort. The main etiology was ischemic heart disease (56%) followed by dilated cardiomyopathy (14%). Medical treatment was optimized during follow-up (Table 1). Supplementary Table 1 compares patients included and not included (lack of a second echocardiogram) to address group bias.

A total of 4183 echocardiograms were performed during the study period. The prospective echocardiography schedule and the distribution of echocardiograms performed per patient (mean 3.6±1.7) are shown in Supplementary Figures 1 and 3. Mean LVEF values were 30%±8 (n=1160), 38%±12 (n=1024), 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, 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=0.005). 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)
compared to patients with longer HF duration at the baseline visit, followed by a plateau
(Figure 1 B) (P for both trajectories <0.001; P between groups <0.001).

Figure 2 shows LVEF trajectories relative to HF etiology. Ischemic HF patients
showed a moderate LVEF increase at one year, with a relative plateau thereafter. Non-
ischemic HF showed a more pronounced bump at one year and a more prolonged
increase during follow-up versus ischemic HF (~7–10 LVEF points; P for both
trajectories <0.001; P between groups <0.001) (Figure 2A). The greatest LVEF increase
was observed in hypertensive HF (Figure 2B). Among non-ischemic etiologies, the
LVEF increase tended to be more limited in time (3 years) in toxic (chemotherapy) and
valvular HF, while 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 for all trajectories <0.001).

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. Remarkably, at 15
years, HFmrEF was associated with slightly lower LVEF than HFrEF (P<0.008) (P for both trajectories <0.001; P between groups <0.001) (Figure 3A). The evolution of HFrEF showed that 56% of patients did not move out of the HFrEF category, while 21% and 23% moved to the HFmrEF and HF with preserved ejection fraction (HFpEF) categories, respectively. By contrast, among patients with HFmrEF, patients at the end of follow-up were quite equally distributed across HFrEF (25%), HFmrEF (39%), and HFpEF (36%) (Figure 3B).

Women showed higher LVEF than men both at baseline (P<0.001) and up to 9 years (P=0.001) (Figure 4). In addition, LVEF recovery was significantly higher in women compared to 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 for both trajectories <0.001; P between genders <0.004).

Remarkably, patients who died during each study period had lower previous LVEF than survivors (Figure 5A) and also worse LVEF dynamics in the preceding immediate study period (changes between the two previous LVEF) during most of the follow-up (Figure 5B).

DISCUSSION

The present study stands out for the 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 remains too high, with a 15-year mortality of 72%, yet the majority of patients alive were adequately studied. The two 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 a LVEF rise up to a decade and a slow LVEF decline thereafter. Second, a declining LVEF in the preceding period is associated with higher mortality (Central Illustration). We discuss each of these aspects below. Most studies of HF with depressed systolic function, including clinical trials and observational studies, generally report only one 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), and far from the benefit achieved with current therapies. The transient nature of LVEF recovery has been previously described. Cioffi et al.,\(^7\) in a small prospective study, observed that LVEF normalization was subsequently lost in 55\% of patients in the following 2 years. De Groote et al.\(^8\) reported that 25\% of patients with LVEF recovery after \(\beta\)-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 experienced an initial LVEF rise. Our findings confirm these earlier data, but in a large cohort prospectively followed over 15 years. We observed an 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 aetiologies.

A remarkable finding of the current study is the striking inverted U-shaped LVEF trajectory for patients with HF of non-ischemic 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 β-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists, requires careful consideration. 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 up to 7 years, but survivors in both HF categories progressively overlapped, and HFmrEF even tended to have worse numbers than HFrEF at 15 years. Whether HFmrEF is truly a distinct pathophysiologic entity or rather represents a transitional phenotype is the subject of debate. In many instances, HFmrEF may be a transition phenotype of patients with HFrEF who are recovering. 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. Our long-term data support the characterization of HFmrEF as just a snapshot on the way towards recovering or declining LV systolic function rather than as a stable phenotype. Indeed, as shown in Figure 3, only slightly more than one-third of patients initially classified as HFmrEF remained in that category during the full-term follow-up, while one third evolved to HFpEF and 25% were categorized as 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 ourselves) and others awaiting more evidence and guideline recommendations.
Sex differences were also observed, including better LVEF dynamics among women, who had higher baseline LVEF and subsequent 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 may be among the explanations.\textsuperscript{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 β-blockers and angiotensin-affecting drugs in reverse remodeling are partially lost in the long-term because of a certain degree of ‘drug resistance’ remains elusive. The long-term effect of sacubitril/valsartan eventually may 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 “survival effect”, very long-term survival was accompanied with a progressive LVEF decay, variable in intensity depending on the discussed clinical covariates.

This study has some 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 and not at the discretion of the patient’s physician, and were not retrospectively analyzed. We acknowledge that intra- and inter-observer variability of echo-derived LVEF is \textasciitilde{}5%. However, taking into account the large number of studies performed, we may assume that such variability was randomly distributed during follow-up. Further, contrast echocardiography may be superior in the evaluation of LV 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 one-year echocardiography data available for analysis. At present there is lack of evidence-based data on what is the best treatment for HFmrEF patients, but in our HF clinic we managed them as HFrEF.

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. Of note, a common protocol of treatment was applied to all patients, thus limiting possible bias introduced by different management strategies or treatment protocols.

**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 are variable depending on HF etiology, HF duration, ESC classification, and sex. In this study, non-ischemic HF patients showed a pattern of temporal myocardial remission without full recovery (except most alcohol-derived). Patients with ischemic HF showed LVEF increase mainly during the first year and then remained stable. A declining LVEF in the preceding period was associated with higher mortality.
PERSPECTIVES

Competency in Medical knowledge

LVEF trajectories vary in HF depending on a number of disease modifiers (etiology, HF duration, sex), but an inverted U-shape pattern with lower LVEF at both ends of the distribution emerged. Remarkably, a declining LVEF in the preceding period was associated with higher mortality.

Translational Outlook

Contemporary medical treatment of HF with depressed ejection fraction is associated with a marked LVEF early rise, a plateau during a decade and a slow decline thereafter. Further research is needed to extend myocardial recovery over a longer temporal period and to reduce excess mortality.
REFERENCES


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FIGURE LEGENDS

Figure 1: **Title:** Loess splines curves of long-term LVEF trajectories.

**Caption:** **Panel A:** Total cohort. P for trajectory changes on LVEF <0.001.

**Panel B:** comparison between patients with HF duration ≤1 year (orange) vs >1 year (blue). P for trajectory changes on LVEF <0.001 for both groups. P for comparison between groups <0.001. Shaded regions displayed around curves represent the confidence interval at level = 0.95.

Figure 2: **Title:** Loess splines curves of long-term LVEF trajectories based on etiology.

**Caption:** **Panel A:** Ischemic (orange) vs non-ischemic (blue) etiology of HF. P value for trajectory changes on LVEF <0.001 for both groups. P for comparison between groups <0.001.

**Panel B:** different non-ischemic etiologies: upper-left, Dilated Cardiomyopathy; upper mid, Hypertensive Cardiomyopathy; upper-right, Alcohol-induced; lower-left, Drug-induced; lower-mid, Valvular disease. P for trajectory changes on LVEF <0.001 for all etiologies. Taking Dilated Cardiomyopathy as 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 displayed around curves represent the confidence interval at level = 0.95.
Figure 3. Title: LVEF Evolution according to European Society Cardiology classification: HFrF vs HFmrEF

Caption: Panel A: Loess splines curves of long-term LVEF trajectories (HFrEF orange, HFmrEF blue). P for trajectory changes on LVEF <0.001 for both groups. P for comparison between groups <0.001. Shaded regions displayed around curves represent the confidence interval at level = 0.95.

Panel B: Distribution of patients into HFrEF and HFmrEF class at baseline and at the last observation for every patient. Left pair of bars HFrEF patients at baseline; Right pair of bars HFmrEF at baseline.

Figure 4: Title: Loess splines curves of long-term LVEF trajectories based on gender.

Caption: Women (orange) vs. men (blue). P for trajectory changes on LVEF <0.001 for both genders. P for comparison between genders <0.004. Shaded regions displayed around curves represent the confidence interval at level = 0.95.

Figure 5. Title: LVEF and survival.

Caption: Panel A: LVEF in the last echocardiogram previous to the analyzed study period vital status. Orange color represents those patients who died in the following study period and blue color those who survive for this entire period. The central box represents the values from the lower to the upper quartile; the middle line represents the median; the
whiskers extend from the minimum to the maximum value, excluding outside and far out values which are not displayed.

**Panel B:** Changes between the last two echocardiograms previous to the analyzed study period vital status. Orange color represents those patients who died in the following study period and blue color those who survive for this entire period.

**Central Illustration. Title:** 15-year LVEF trajectories and dynamics.

**Caption:** Long-term LVEF trajectories of the total cohort showed a marked LVEF rise during the first year, maintained up to a decade, and manifested a slow LVEF decline thereafter. The early improvement was related to etiology (higher in non-ischemic patients), HF duration (higher in <12 months duration) and sex (higher in women). LVEF dynamics are related to outcome: patients who died had worse dynamics in the preceding immediate study period than patients who remained alive (less initial improvement and higher declining afterwards).
Table 1. Demographic, clinical, and therapeutic characteristics of patients

<p>| Age, years | 64.9 ± 12.3 | 1160 |
| Male | 887 (76.5) | 1160 |
| White | 1153 (99.4) | 1160 |
| Etiology | 1160 |
| Ischaemic heart disease | 662 (57.1) |
| Dilated cardiomyopathy | 160 (13.8) |
| Hypertensive | 82 (7.1) |
| Alcohol | 68 (5.9) |
| Drugs | 35 (3.0) |
| Valvular | 70 (6.0) |
| Other | 83 (7.2) |
| HF duration, months | 6 (1–40) |
| NYHA class | 1160 |
| I | 60 (5.2) |
| II | 817 (70.4) |
| III | 277 (23.9) |
| IV | 6 (0.5) |
| LVEF, % | 30.4 ± 8.4 |
| LV end-diastolic diameter, mm | 61.4 ± 8.3 |
| LV end-systolic diameter, mm | 49.3 ± 9.5 |
| Diabetes | 461 (40.0) |
| Hypertension | 713 (61.5) |
| Anemia* | 497 (43.0) |
| Renal insufficiency† | 471 (41.0) |
| Atrial fibrillation/flutter | 203 (17.5) |
| LBBB | 155 (13.4) |
| Heart rate | 70.7 ± 14.6 |
| Blood pressure | 125.5 ± 21.7 |
| BMI, Kg/m2 | 27.0 (24.3-30.3) |
| NTproBNP, ng/L | 1623 (709–3709) |
| Treatments (Baseline), n (%) | 1160 |
| ACEI or ARB | 1063 (91.6) |
| Beta-blocker | 886 (76.4) |
| MRA | 391 (33.7) |
| Loop diuretic | 873 (75.3) |
| Digoxin | 258 (22.2) |
| Ivabradine | 72 (6.2) |
| Sacubitril/Valsartan | 0 (0) |
| CRT | 0 (0) |
| ICD | 74 (6.4) |
| Treatments (F-U), n (%) | 1160 |
| ACEI or ARB | 1084 (93.4) |
| Beta-blocker | 1094 (91.6) |
| MRA | 778 (67.1) |</p>
<table>
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<th>Treatment</th>
<th>Count (Percentage)</th>
<th>Median (IQR)</th>
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<td>Loop diuretic</td>
<td>1062 (91.6)</td>
<td>1160</td>
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<tr>
<td>Digoxin</td>
<td>477 (41.1)</td>
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<tr>
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<tr>
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Data in mean ± SD, median (IQR) or n (%)

*According to W.H.O. criteria (<13 g/dl in men and <12 g/dl in women)

†eGFR (CKD-EPI equation) < 60 ml/min/1.73 m²

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; CRT: cardiac resynchronization therapy; eGFR: estimated glomerular renal filtration (CKD-EPI equation); F-U: follow-up; HF: heart failure; ICD: implantable cardiac defibrillator; LBBB: left bundle branch block. LVEF: left ventricular ejection fraction; MRA: mineralcorticoid receptor antagonist; NYHA: New York Heart Association; NTproBNP: N-terminal pro-brain natriuretic peptide.