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Clinical characteristics and one-year change in ejection fraction and outcomes in patients with heart failure with mid-range ejection fraction

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Clinical characteristics and one-year change in ejection fraction and outcomes in patients with heart failure with mid-range ejection fraction

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ABSTRACT

Objectives: The aim of this study was to analyse baseline characteristics and outcome of patients with heart failure and mid-range left ventricular ejection fraction (HFmrEF, left ventricular ejection fraction (LVEF) 40–49%) and the effect of 1-year change in LVEF in this group.

Setting: Multicentre prospective observational study of ambulatory HF patients follow-up at 4 university hospitals with dedicated HF units.

Participants: Fourteen percent (n=504) of the 3580 patients included had HFmrEF.

Interventions: Baseline characteristics and 1-year outcomes and LVEF were collected. All-cause death, HF hospitalization and the composite end-point were the primary outcomes.

Results: Median follow-up was 3.66 [1.69-6.04] years. All-cause death, HF hospitalization and the composite end-point were 47%, 35% and 59%, respectively. Outcomes were worse in HFpEF (LVEF>50%), without differences between HFrEF (LVEF<40%) and HFmrEF. After multivariable Cox regression analyses, no differences in all-cause death and the composite end-point were seen between the three groups. HF hospitalization and cardiovascular death were not statistically different between patients with HFmrEF and HFrEF. At 1-year follow-up, 62% of patients with HFmrEF had LVEF measured: 24% had LVEF<40%, 43% maintained LVEF 40-49% and 33% had LVEF>50%. While change in LVEF as continuous variable was not associated with better outcomes, those patients who evolve from HFmrEF to HFpEF did have a better outcome.

Conclusions: Patients with HFmrEF have a clinical profile in-between HFpEF and HFrEF, without differences in all-cause mortality and the composite end-point between the three groups. At 1-year, patients with HFmrEF exhibited the greatest variability in LVEF and this change was associated with survival.

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Key words: heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; Heart failure with mid-range ejection fraction; Prognosis; echocardiography; ejection fraction; recovered

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SRENGHTS AND LIMITATIONS OF THIS STUDY

- Cohort study of heart failure (HF) patients followed up at 4 hospitals with a dedicated HF unit.
- The hospitals varied from community oriented hospitals to reference centres with transplant and ventricular assist devices programs.
- Baseline characteristics of patients were different among the 4 hospitals, which allow an easier generalization of the results.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

DATA SHARING STATEMENT:

Additional unpublished data might be available to those completing the request for research upon acceptance by the GICCAT group.

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INTRODUCTION:

Despite the improvement in knowledge and treatment of heart failure (HF) in the last decades, HF is still a prevalent disease with a grim prognosis[1] and to which considerable healthcare resources are dedicated[2]. Much of the research to date has focused on patients with HF and reduced ejection fraction (HFrEF) and so far pharmacological and invasive treatments have only shown to be useful in this group of patients[3]. Furthermore, definition of HF with preserved ejection fraction (HFpEF) varies widely in registries and in randomized control trials (from left ventricular ejection fraction (LVEF) >40% to > 55%)[4] and hence a gray zone of patients with LVEF ranging 40 to 50% has hardly been studied. For this reason, the last 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF included this new mid-range group in the classification of HF in order to stimulate research in this subpopulation of patients[3]. In patients with HFrEF (LVEF<40%) an improvement in LVEF has been associated with better outcomes[5]. Whether this is also true in patients with mid-range EF (HFmrEF) is unknown.

Hence, the aim of this study was to analyse the baseline characteristics and outcome of patients with HFmrEF compared to patients with HFpEF (LVEF>50%) and HFrEF and to analyse the effect of 1-year change in LVEF in patients with HFmrEF on outcome.

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METHODS

Study population

This was a prospective observational study of HF patients followed at 4 university hospitals with a dedicated Heart Failure Unit. Patients were consecutively enrolled from August 2001 to June 2015 and HF was diagnosed following the European Society of Cardiology (ESC) guidelines[3]. Baseline demographic, clinical and echocardiographic data were collected. Patients were classified in three groups according to the new ESC Guidelines for the diagnosis and treatment of acute and chronic HF: HFrEF, HFmrEF and HFpEF[3]. Changes in medical therapy over time were not collected.

Data on 1-year LVEF were also collected when available. Follow up echocardiograms were performed as per each institutional protocol. All patients were followed up at regular intervals. Those who failed to attend the clinic appointment were contacted by telephone and hospital and primary care records were reviewed in order to assess vital status and HF hospitalizations. The main outcome was recorded as death from all causes, HF hospitalization and a composite end-point of all-cause death and HF hospitalization. Cardiovascular (CV) death was also analysed. A death was considered of CV origin if it was caused by HF, sudden death, acute myocardial infarction, stroke, CV procedural, or other CV causes.

The study was approved by the Ethics Committees of the participating hospitals, and all patients gave written informed consent on their initial visit.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), depending on whether data distribution was normal (assessed by normal Q–Q plots); categorical variables were expressed as percentages. A comparative analysis between variables was carried out using Chi-

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square test (categorical variables) and Student's t-test or Mann–Whitney U-test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables. P-value adjustment for multiple testing was performed by Tukey (normal-distribution) or Benjamini & Hochberg method (otherwise). Kaplan-Meier survival curves were compared by the log-rank test. Multivariate analysis was performed using Cox proportional hazard regression (Cox) including center as strata. In all analyses involving CV death and HF hospitalization, a competing risks strategy by the Gray method was adopted6, considering non-CV death as the competing event for CV death, and all-cause death for HF hospitalization. HFrEF was used as the reference category. The analyses were performed with R (version 3.3.2) R: A Language and Environment for Statistical Computing (Vienna, Austria). We considered P-values <0.05 from two-sided tests to indicate statistical significance.

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RESULTS:

Baseline clinical characteristics

Baseline clinical characteristics and treatment were categorized according to LVEF and are summarized in Table 1. Fourteen percent (n=504) of the 3580 patients included in the study had HFmrEF, 62% had HFrEF and 24% HFpEF. In the whole cohort mean age was 68±13 years, 62% were men and mean LVEF was 38±16%. Baseline characteristics of patients with HFmrEF were in-between those of HFpEF and HFrEF. Use of neurohormonal treatment was higher in patients with HFrEF and HFmrEF whereas the use of loop diuretic was highest in the HFpEF group. The four cohorts were clinically different (see the Supplementary material online, Table S1, describing the baseline characteristics according to hospital).

Follow-up Events

During a median follow-up of 3.66 (1.69-6.04) years, all-cause death, HF hospitalization and the composite end-point were 47%, 35% and 59%, respectively (Table 2). The cause of death was CV in 24.7% of patients, without differences in the three groups (overall p=0.068). Outcomes were worse in HFpEF, without differences between HFrEF and HFmrEF (Figure 1). In multivariable Cox regression analyses, no differences in all-cause death and composite end-point were seen between the three groups. HF hospitalization and CV death were not statistically different between patients with HFmrEF and HFrEF, although a tendency (p=0.068) towards a lower CV mortality in HFmrEF was observed (Table 3). On the other hand, HFpEF patients had significantly higher HF hospitalization and lower CV death (Table 3).

Changes in LVEF

Of the 1971 patients with HFrEF alive at 1 year, 67% had an echocardiogram performed: 62% still had LVEF<40% and 21% had LVEF 40-50%. In this group, after

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adjustment for age, sex and baseline EF, hazard ratios (HR) for survival for change in LVEF was 0.97 (95% CI 0.96-0.98, p<0.001).

LVEF of patients with HFmrEF (analyzed in 61% of the 438 patients alive at 1-year) had the greatest variation: 24% had reduced LVEF, 43% maintained LVEF 40-49% and 33% had LVEF>50%. Figure 2 shows Kaplan-Meier curves for long-term outcome for changes of LVEF in HFmrEF. There were no differences in mortally between patients who remained in HFmrEF group and those who changed to HFrEF, while survival was significantly higher in those patients who evolved to the HFpEF group (p=0.026). Compared with patients whose LVEF improved enough to move to the HFpEF group, those who remained in the HFmrEF and HFrEF had higher all-cause mortality after adjustment for age, sex and baseline LVEF (HR 1.96 (95% CI 1.08-3.54, p=0.027 and HR 2.01 (95% CI 1.04-3.86, p=0.037), respectively). As a continuous variable, however, and after adjustment for age, sex and baseline LVEF, HR for survival for change in LVEF was 0.99 (95% CI 0.96-1.01, p=0.229). Baseline characteristics of patients who evolved to HFpEF were similar to that of those that remained in HFmrEF or went to HFrEF except for a higher proportion of women (38% vs. 23%, p=0.021) and non-ischemic etiology (61% vs. 38%, p=0.001), higher diastolic blood pressure (76±11 vs. 72±12 mmHg, p=0.009) and eGFR (70±24 vs. 63±27 mL/min, p=0.028) but lower NTproBNP (901 [450-1690] ng/L vs. 1494 [593-4456], p=0.013). Baseline LVEF was lower (44±3% vs. 42±2, p<0.001). Interestingly, treatment was similar in both groups, with a high use of beta blockers (93% of all patients), ACEI/ARB (83%) and MRA (48%).

Finally, among patients with HFpEF alive at one year, only 288 (40%) had LVEF measured at 1 year follow-up, and the majority (85%) of them still had LVEF >50%. After adjustment for age, sex and baseline EF, HR for survival for change in LVEF in this group was 0.99 (95% CI 0.97-1.01, p=0.283).

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DISCUSSION:

Patients with HFmrEF are a small group in the spectrum of HF patients and their clinical characteristics did not allow differentiating them from HFpEF or HFrEF patients. Moreover, all-cause mortality was not different from that of HFpEF or HFrEF. CV mortality, however, tended to be lower in HFmrEF patients than in HFrEF patients. Interestingly, change in 1-year LVEF in this group was broader (24% had a decrease in LVEF and 33% had LVEF>50%). While change in LVEF fraction as continuous variable was not associated with better outcomes, those patients who evolve from HFmrEF to HFpEF actually did have a better outcome.

Baseline clinical characteristics

Prevalence of HFmrEF in our study was 14%, similar to other studies carried out in hospitalized (prevalence between 13-26%)[7-11] and ambulatory (9-17%)[12-16] HF patients. Consistent with other studies, clinical characteristics of patients with HFmrEF did not allow for a clear clinical differentiation of this group. Age and prevalence of women were higher in HFmrEF than in HFrEF but lower than in HFpEF. This finding is consistent across different studies[7,9,10,13-18]. Some co-morbidity such as diabetes mellitus, dyslipidemia and COPD were not different between the three groups. In patients with HFmrEF the presence of anemia, chronic kidney disease and NYHA class III-IV was similar than in HFrEF but was lower than in HFpEF. Interestingly, NTproBNP was not different between HFmrEF and HFpEF but was lower than in HFrEF. Etiology of HF was also different between the three groups, with a predominant ischemic cause in HFrEF and HFmrEF and hypertensive in HFpEF. Similar results have been described in other studies, and, although some differences can be found in the distribution of comorbidities among studies[7-10,12-15,17,18,19], the overall perception is that it is not possible to identify a clear pattern of clinical characteristics that defines HFmrEF.

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Follow-up Events

All-cause mortality and HF hospitalization were similar in HFrEF and HFmrEF (45.8% vs 43.8%, p=0.448) but were lower than in HFpEF (52.6%, overall p=0.002). However, in multivariable Cox regression analyses with competing risk, HFpEF performed worse than those with HFmrEF and HFpEF, relative to HF hospitalization but had lower CV mortality. Whilst some studies have shown no differences in outcomes among the three groups[7-10,13], other authors have found different results, with a higher mortality in HFmrEF compared to HFpEF in ambulatory HF patients[12] and, contrary to our results, a higher HF hospitalization in HFrEF compared to HFmrEF and HFpEF[18]. Interestingly, we found similar all-cause death between HFrEF and HFmrEF patients, but a trend to lover CV mortality in HFmrEF in the latter.

Changes in LVEF

At 1-year follow-up, LVEF of patients with HFmrEF had the greatest variation: 24% had reduced LVEF, 43% maintained LVEF 40-49% and 33% had LVEF>50%. Remarkably, in this group, change in LVEF as continuous variable was not associated with survival but when the improvement in LVEF was enough to move the patient from HFmrEF to HFpEF, survival was significantly better. Women and non-ischemic etiology were more frequent in patients who moved to HFpEF and that has been shown in other studies[20]. Although treatment has been associated with improvement in LVEF[21-23] we did not see any difference in treatment between patients who move to HFpEF and those who remained in HFmrEF or went to HFrEF. However, this lack of difference might be explained by the high use of Class I medication in our population.

The apparent paradox of absence of a clear difference in long-term prognosis in patients according to the three groups of LVEF can be plausibly disentangled. On the one hand, LVEF measured by echocardiography is an imperfect measure to determine left ventricular systolic function as it only captures one part of the whole biomechanics

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of cardiac function and exhibits important variability[24]. Moreover, impairment of left ventricular systolic function is also present in patients with HFpEF, even though their LVEF might be normal[25]. On the other hand, cut-offs used to define the three groups (HFrEF, HFmrEF and HFpEF) are arbitrary[3]. Finally, LVEF is a dynamic measure that can vary with treatment[22,23] and during follow-up[16,21,22]. Depending on the cut-off used (LVEF 40% vs. 50%), up to 50% of patients with HFpEF were patients with previously reduced LVEF[26,27] and patients with recovered LVEF had a better prognosis compared to those with preserved or reduced LVEF[19,20,21,26-28] and with those who did not improve LVEF[5]. Although it was less frequent, patients with HFpEF also showed variability in LVEF during follow-up (only 15% of HFpEF patients had LVEF<50% at 1-year follow-up in our study). Dunlay et al. showed that among HFpEF patients, 21.1% had an EF<50% around 1 year after diagnosis, and this increased to 32.5% in those with an echo performed from 4 to 6 years after diagnosis[21], and similar results were seen in other studies[16,22]. In the present study, change in LVEF in HFpEF was not independently associated with all-cause mortality. In HFmrEF, patients whose LVEF improved enough to move to HFpEF outcome was better but when LVEF did not move or worsened, prognosis was worse, consistently with other studies that showed that irrespective of baseline group, the transition to HFrEF was associated with increased all-cause mortality[16].

Taken together, the results of the present and previous studies show that the classification of patients in HF with preserved, mid-ranged and reduced LVEF is not static. In other words, many patients with HFmrEF might be either recovered HFrEF patients or, probably to a lesser extent, patients with worsened HFpEF and this fact might explain the difficulty in clinically characterizing them properly and might explain the lack of differences found in all-cause mortality between the three groups. Hence, the only reason to classify patients according to their LVEF would be to identify patients in whom pharmacological and device treatments have proved to improve prognosis.

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Limitations:

Follow-up echocardiograms were not done at pre-specified intervals in all patients. This might have been a source of bias because the decision to perform a follow-up echocardiogram may have been influenced by clinical status, age and baseline LVEF. Dunlay et al report that their patients had a median of 2 echocardiograms during follow up and mean time from initial to final EF measurement was around 3 years but these authors did not report how many patients had an echocardiogram done at 1-year follow up[21]. In another study, 43% of patients with a primary hospital discharge diagnosis for HF did not have 2 or more LVEF tests ≥ 30 days apart during the study period[22]. Hence, considering that in the present study two thirds of patients had an echocardiogram done at 1-year follow up, we think that results are consistent with common clinical practice.

NT-proBNP was missing in 25% of our patients and therefore this biomarker was not included in the multivariable analysis. Consistently with our results, van Veldhuisen et al. showed that BNP levels were lower in patients with HFpEF than in HFrEF. For a given BNP level, that study showed that the prognosis in patients with HFpEF was similar than those with reduced LVEF[29].

Finally, the baseline characteristics of the patients included in the 4 hospitals are remarkably different. Although that may be seen as a limitation, the inclusion of different type of HF patients allowed us to better characterize this population, combining patients followed up in centres with different degree of specialization (advanced HF centres and community oriented hospitals), thus including patients that would have been lost if only centres with similar characteristics were analysed.

CONCLUSIONS:

Patients with HFmrEF have a clinical profile in between HFpEF and HFrEF and there were no differences in all-cause mortality and the composite end-point between the

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three groups. At 1-year follow-up patients with HFmrEF had the greatest variability (up and down) in LVEF but change in LVEF was not associated with survival, except when patients actually evolve to HFpEF group. The classification of patients in HF with preserved, mid-ranged and reduced LVEF is not static and thus, the only reason to classify patients according to their LVEF would be to identify patients in whom disease-modifying therapies are useful to improve prognosis.

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FIGURE LEGENDS:

Figure 1: Kaplan-Meier curves for long-term outcome divided by LVEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence; C, composite end-point cumulative survival).

Figure 2: Kaplan-Meier curves for long-term outcome for changes of LVEF in the HFrmEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence).

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Table 1 Baseline clinical characteristics and treatment categorized according to LVEF.

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	All N=3580	HFrEF N=2232 (62%)	HFmrEF N=504 (14%)	HFpEF N=844 (24%)	P value *	P value **	P value ***	N
Male	2397 (67.0)	1689 (75.7)	337 (66.9)	371 (44.0)	<0.001	<0.001	<0.001	3580
Age	68.2±12.7	66.2±12.5	68.1±12.9	73.5±11.4	<0.001	0.003	<0.001	3580
LVEF	38.3±16.0	28.0±6.9	43.5±2.9	62.5± 8.3	<0.001	<0.001	<0.001	3580
Etiology:					<0.001	<0.001	<0.001	3579
ischemic	1600 (44.7)	1174 (52.6)	261 (51.8)	165 (19.5)				
dilated	552 (15.4)	450 (20.2)	58 (11.5)	44 (5.21)				
hypertensive	592 (16.5)	169 (7.58)	72 (14.3)	351 (41.6)				
valvular	321 (8.97)	131 (5.87)	45 (8.93)	145 (17.2)				
other	514 (14.4)	307 (13.8)	68 (13.5)	139 (16.5)				
Heart rate	72.7± 14.8	72.8±14.9	70.8± 14.3	73.8±14.6	0.001	0.005	<0.001	3577
Hypertension	2485 (69.4)	1434 (64.2)	366 (72.6)	685 (81.2)	<0.001	<0.001	<0.001	3580
Diabetes mellitus	1547 (43.2)	956 (42.8)	210 (41.7)	381 (45.1)	0.386	0.669	0.235	3580
COPD	721 (20.1)	427 (19.1)	103 (20.4)	191 (22.6)	0.096	0.544	0.381	3580
Dyslipidemia	1843 (51.5)	1158 (51.9)	263 (52.2)	422 (50.0)	0.611	0.942	0.472	3580
Atrial fibrillation	999 (27.9)	435 (19.5)	158 (31.3)	406 (48.2)	<0.001	<0.001	<0.001	3579
BMI, Kg/m2	27.8±5.30	27.3±4.93	28.2±5.30	28.9±6.01	<0.001	<0.001	0.045	3528
Sodium, mmol/L	139±4.33	139±4.67	140±3.50	140± 3.63	<0.001	<0.001	0.730	3556
Anemia	1231 (34.9)	656(29.9)	184(37.1)	391(46.8)	<0.001	0.002	0.001	3580
NT-proBNP, ng/L	1638 (697;3937)	1898 (769;4465)	1484 (532;3866)	1320 (635;2818)	<0.001	<0.001	0.518	2705
eGFR, mL/min/1.73m2	60.4±25.4	62.4±25.4	60.4±26.5	55.2±23.8	<0.001	0.125	<0.001	3562
NYHA class III–IV	1293 (36.1)	746 (33.4)	172 (34.1)	375 (44.4)	<0.001	0.808	<0.001	3579
Treatment:								
ACEI or ARB	2992 (83.9)	1992 (89.5)	412 (82.1)	588 (70.1)	<0.001	<0.001	<0.001	3567
Beta-blockers	3094 (86.4)	2040 (91.4)	448 (88.9)	606 (71.8)	<0.001	0.092	<0.001	3580

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MRA	1890 (52.8)	1447 (64.8)	219 (43.5)	224 (26.5)	<0.001	<0.001	<0.001	3580
Loop diuretics	3189 (89.1)	2002 (89.7)	423 (83.9)	764 (90.5)	<0.001	<0.001	<0.001	3580
Digoxin	959 (27.7)	675 (30.8)	106 (21.7)	178 (22.5)	<0.001	<0.001	0.788	3467
ICD	396 (11.1)	359 (16.1)	26 (5.16)	11 (1.31)	<0.001	<0.001	<0.001	3578
CRT	234 (6.54)	213 (9.54)	16 (3.17)	5 (0.59)	<0.001	<0.001	0.001	3580
Anticoagulants	1684 (47.0)	969 (43.4)	239 (47.4)	476 (56.4)	<0.001	0.113	0.002	3580

Data are mean ± standard deviation, median (interquartile range) or n (%). *P-values for the comparison of all three groups (null hypothesis: all three groups have the same characteristics). **P-value only applies to the comparison of HFrEF vs. HFmrEF. ***P-value only applies to the comparison of HFpEF vs. HFmrEF. Anemia was defined as a hemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide. HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction; HFpEF, heart failure with preserved left ventricle ejection fraction.

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Table 2: Mortality, cause of death and heart failure hospitalization during follow-up

	All N=3580	HFrEF N=2232 (62%)	HFmrEF N=504 (14%)	HFpEF N=844 (24%)	P value *	P value **	P value ***	N
All-cause death	1688 (47.2)	1023 (45.8)	221 (43.8)	444 (52.6)	0.001	0.448	0.003	3580
Cause of death					<0.001	0.164	0.011	3580
HF	458 (12.8)	269 (12.1)	58 (11.5)	131 (15.5)				
Sudden death	126 (3.52)	101 (4.53)	13 (2.58)	12 (1.42)				
Other cardiovascular	196 (5.47)	122 (5.47)	29 (5.75)	45 (5.33)				
Non cardiovascular	500 (14.0)	265 (11.9)	72 (14.3)	163 (19.3)				
Unknown	408 (11.4)	266 (11.9)	49 (9.7)	93 (11.0)				
HF hospitalization	1259 (35.2)	724 (32.4)	157 (31.2)	378 (44.8)	<0.001	0.613	<0.001	3580
Composite end-point	2113 (59.0)	1277 (57.2)	272 (54.0)	564 (66.8)	<0.001	0.201	<0.001	3580

Data are n (%). *P-values for the comparison of all three groups (null hypothesis: all three groups have the same characteristics). **P-value only applies to the comparison of HFrEF vs. HFmrEF. ***P-value only applies to the comparison of HFpEF vs. HFmrEF.

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Table 3: Multivariable Cox regression analyses with hospital as strata for all-cause death, HF hospitalization and composite end-point

	All-cause death		HF hospitalization		Composite end-point (All-cause death + HF hospitalization)		CV death	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
HFrEF	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
HFmrEF	0.93 (0.80-1.08)	0.338	1.00 (0.84-1.20)	0.98	0.94 (0.82-1.07)	0.358	0.80 (0.64-1.01)	0.061
HFpEF	0.93 (0.81-1.06)	0.265	1.18 (1.02-1.38)	0.032	0.95 (0.84-1.06)	0.362	0.75 (0.62-0.92)	0.006
Female	0.75 (0.67-0.84)	<0.001	-		0.85 (0.77-0.94)	0.002	0.75 (0.64-0.88)	<0.001
Age	1.03 (1.03-1.04)	<0.001	-		1.02 (1.02-1.03)	<0.001	1.03 (1.02-1.04)	<0.001
Heart rate	1.00 (1.00-1.01)	0.013	-		1.00 (1.00-1.01)	0.008	-	
DBP	0.99 (0.99-1.00)	0.002	0.99 (0.99-1.0)	0.044	0.99 (0.99-1.00)	0.001	0.99 (0.98-0.99)	<0.001
Dyslipidemia	0.86 (0.78-0.96)	0.004	1.25 (1.10-1.41)	<0.001	-		-	
DM	1.30 (1.17-1.44)	<0.001	1.22 (1.08-1.37)	0.002	1.27 (1.16-1.39)	<0.001	1.27 (1.11-1.47)	<0.001
COPD	1.32 (1.17-1.48)	<0.001	1.27 (1.10-1.47)	<0.001	1.30 (1.17-1.45)	<0.001	-	
BMI	0.98 (0.97-0.99)	<0.001	-		-		-	
Sodium	-		-		-		0.99 (0.97-1.00)	0.024
Hemoglobin	0.93 (0.90-0.96)	<0.001	0.90 (0.87-0.93)	<0.001	0.91 (0.89-0.93)	<0.001	0.93 (0.89-0.97)	0.001
eGFR	0.99 (0.99-1.00)	<0.001	0.99 (0.99-0.99)	<0.001	0.99 (0.99-1.00)	<0.001	0.99 (0.99-0.99)	<0.001
NYHA class III-IV	1.62 (1.46-1.80)	<0.001	1.34 (1.18-1.51)	<0.001	1.54 (1.40-1.69)	<0.001	1.61 (1.39-1.86)	<0.001
ACEI or ARB	0.70 (0.62-0.81)	<0.001	-		0.74 (0.65-0.83)	<0.001	-	
Beta-blockers	0.60 (0.53-0.69)	<0.001	-		0.70 (0.62-0.79)	<0.001	0.60 (0.49-	<0.001

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							0.72)	
Loop diuretics	1.28 (1.04-1.57)	0.020	2.97 (2.18-4.06)	<0.001	1.61 (1.33-1.94)	<0.001	1.88 (1.32-2.67)	<0.001
CRT	0.70 (0.55-0.89)	0.003	-		-		-	
ICD	-		-		-		0.77 (0.60-0.98)	0.032
MRA	-		1.18 (1.03-1.34)	0.014	-		-	
Digoxin	-		1.48 (1.29-1.69)	<0.001	-		1.26 (1.08-1.47)	0.004
Anticoagulants	-		-		-		-	
Hypertension	-		-		1.12 (1.01-1.25)	0.033	-	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate (CKD-EPI equation); MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction ; HFpEF, heart failure with preserved left ventricle ejection fraction.

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AUTHOR'S CONTRIBUTION:

All authors fulfill the ICMJE criteria for authorship:

- Substantial contributions to the conception or design of the work (N.F., J.C.C., J.L., A.B.G., J.V., S.P.), or the acquisition (N.F., E.R., J.G.C., M.A., E.S.G., C.S.E., P.M., S.R., C.E., S.M.), analysis (N.F., J.C.C., J.L., J.V., S.P.) or interpretation of data (N.F., J.C.C., J.L., A.B.G., J.V., S.P., E.R., J.G.C., M.A., E.S.G., C.S.E., P.M., S.R., C.E., S.M.), analysis (N.F., J.C.C., J.L., J.V., S.P.).
- Drafting the work or revising it critically for important intellectual content (all authors).
- Final approval of the version published (all authors).
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors).

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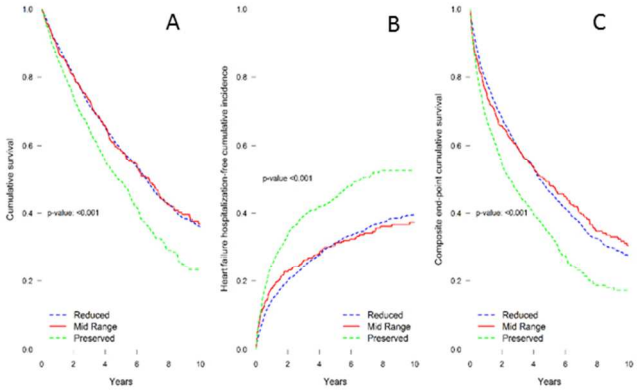

Kaplan-Meier curves for long-term outcome divided by LVEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence; C, composite end-point cumulative survival).

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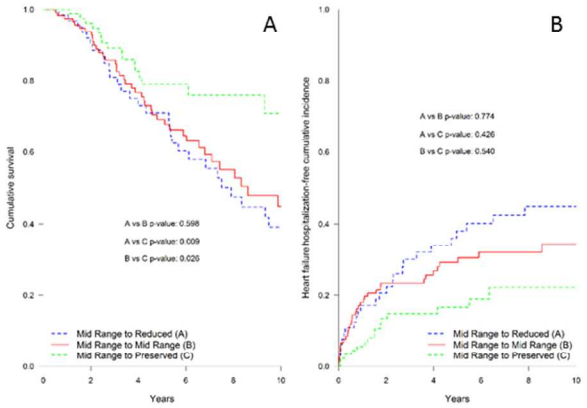

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SUPPLEMENTAL MATERIAL

Table 1: Baseline clinical characteristics for the four hospital cohorts

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	All N=3580	Mar N=1062	H St Pau N=464	Can Ruti N=1835	Bellvitge N=219	P value	N
Male	2232 (62.3)	603 (56.8)	315 (67.9)	1310 (71.4)	169 (77.2)	<0.001	3580
Age	68.2 (12.7)	72.4 (11.3)	67.6 (13.5)	66.8 (12.6)	61.0 (12.1)	<0.001	3580
LVEF	38.3 (16.0)	44.8 (17.0)	42.8 (17.0)	34.2 (13.8)	31.9 (11.7)	<0.001	3580
HF group according to LVEF:						<0.001	3580
HFrEF	2232 (62.3)	471 (44.4)	237 (51.1)	1339 (73.0)	185 (84.5)		
HFmrEF	504 (14.1)	158 (14.9)	75 (16.2)	251 (13.7)	20 (9.13)		
HFpEF	844 (23.6%)	433 (40.8)	152 (32.8)	245 (13.4)	14 (6.39)		
Etiology:						<0.001	3579
ischemic	1600 (44.7)	419 (39.5)	163 (35.1)	928 (50.6)	90 (41.3)		
dilated	552 (15.4)	111 (10.5)	135 (29.1)	241 (13.1)	65 (29.8)		
hypertensive	592 (16.5)	365 (34.4)	50 (10.8)	173 (9.43)	4 (1.83)		
valvular	321 (8.97)	48 (4.52)	77 (16.6)	176 (9.59)	20 (9.17)		
other	514 (14.4)	119 (11.2)	39 (8.41)	317 (17.3)	39 (17.9)		
Heart rate	72.7 (14.8)	74.5 (15.0)	73.4 (14.3)	71.8 (14.8)	70.5 (13.9)	<0.001	3577
Hypertension	2485 (69.4)	857 (80.7)	351 (75.6)	1153 (62.8)	124 (56.6)	<0.001	3580
Diabetes mellitus	1547 (43.2)	503 (47.4)	182 (39.2)	771 (42.0)	91 (41.6)	0.008	3580
COPD	721 (20.1)	238 (22.4)	125 (26.9)	321 (17.5)	37 (16.9)	<0.001	3580
Dyslipidemia	1843 (51.5)	589 (55.5)	238 (51.3)	918 (50.0)	98 (44.7)	0.007	3580
Atrial fibrillation	999 (27.9)	358	208 (44.8)	389 (21.2)	44 (20.2)	<0.001	3579

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		(33.7)					
BMI, Kg/m2	27.8 (5.30)	28.3 (5.70)	28.4 (5.12)	27.4 (5.09)	26.5 (4.80)	<0.001	3528
Sodium, mmol/L	139 (4.33)	140 (3.49)	140 (3.32)	138 (3.63)	139 (9.96)	<0.001	3556
Anemia	1104 (31.3)	420 (39.5)	127(27.4)	603 (33.8)	81 (37.0)	<0.001	3526
NT-proBNP, ng/L	1638 (697;3937)	1577 (688;3996)	1618 (753;3701)	1750 (704;4210)	1420 (572;3198)	0.217	2705
eGFR, mL/min/1.73m2	60.4 (25.4)	56.0 (22.5)	60.4 (25.7)	62.2 (26.4)	67.7 (25.2)	<0.001	3562
NYHA class III–IV	1293 (36.1)	452 (42.6)	172 (37.1)	573 (31.2)	96 (44.0)	<0.001	3579
Treatment:							
ACEI or ARB	2992 (83.9)	793 (74.7)	397 (85.6)	1597 (87.0)	205 (99.5)	<0.001	3567
Beta-blockers	3094 (86.4)	922 (86.8)	373 (80.4)	1611 (87.8)	188 (85.8)	0.001	3580
MRA	1890 (52.8)	406 (38.2)	232 (50.0)	1107 (60.3)	145 (66.2)	<0.001	3580
Loop diuretics	3189 (89.1)	959 (90.3)	385 (83.0)	1654 (90.1)	191 (87.2)	<0.001	3580
Digoxin	959 (27.7)	137 (12.9)	24 (6.84)	732 (39.9)	66 (30.1)	<0.001	3467
ICD	396 (11.1)	24 (2.26)	74 (16.0)	232 (12.6)	66 (30.1)	<0.001	3578
CRT	234 (6.54)	11 (1.04)	33 (7.11)	153 (8.34)	37 (16.9)	<0.001	3580
Anticoagulants	1684 (47.0)	504 (47.5)	210 (45.3)	873 (47.6)	97 (44.3)	0.673	3580

Data are mean ± standard deviation, median (interquartile range) or n (%). P-values for the comparison of all four groups (null hypothesis: all three groups have the same characteristics). Anemia was defined as a hemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass

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index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide. HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction ; HFpEF, heart failure with preserved left ventricle ejection fraction.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – Page 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses – Page 7
Methods		
Study design	4	Present key elements of study design early in the paper – Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – Page 8 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – Page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – Page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Page 8-9
		(*b*) Describe any methods used to examine subgroups and interactions - Page 8-9
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed – Page 8 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage – Page 8, 15
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Page 10, 22-24
		(b) Indicate number of participants with missing data for each variable of interest - Page 22-24
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – Page 10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time – Page 10, 25-27
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – Page 25-27
		(*b*) Report category boundaries when continuous variables were categorized – Page 7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – Page 10-11
Discussion		
Key results	18	Summarise key results with reference to study objectives – Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results - Page 12-14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: a multicentre prospective observational study in Catalonia (Spain).

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	Institute; IDIBELL (Bellvitge Biomedical Reserach Institute
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	Heart failure < CARDIOLOGY, Echocardiography < CARDIOLOGY, Ejection fraction, Prognosis, Recovered

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Clinical characteristics, one-year change in ejection fraction and long-term outcomes in patients with heart failure with mid-range ejection fraction: a multicentre prospective observational study in Catalonia (Spain).

N. Farre[1-3], J. Lupon[3-5], E. Roig[3,5,6], J. Gonzalez-Costello[7,8], J. Vila[9,10], S. Perez[5,10], M. de Antonio[4], E. Sole-Gonzalez[3,5,6], C. Sanchez-Enrique[7,8], P. Moliner[4], S. Ruiz[1,2], C. Enjuanes[2,7,8,11], S Mirabet[3,5,6], A. Bayes-Genis[3-5], J. Comin-Colet[2,7,8,11], on behalf of the GICCAT Investigators.

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ABSTRACT

Objectives: The aim of this study was to analyse baseline characteristics and outcome of patients with heart failure and mid-range left ventricular ejection fraction (HFmrEF, left ventricular ejection fraction (LVEF) 40–49%) and the effect of 1-year change in LVEF in this group.

Setting: Multicentre prospective observational study of ambulatory HF patients followed-up at 4 university hospitals with dedicated HF units.

Participants: Fourteen percent (n=504) of the 3580 patients included had HFmrEF.

Interventions: Baseline characteristics, 1-year LVEF and outcomes were collected. All-cause death, HF hospitalization and the composite end-point were the primary outcomes.

Results: Median follow-up was 3.66 [1.69-6.04] years. All-cause death, HF hospitalization and the composite end-point were 47%, 35% and 59%, respectively. Outcomes were worse in HFpEF (LVEF>50%), without differences between HFrEF (LVEF<40%) and HFmrEF (all-cause mortality 52.6% vs. 45.8% and 43.8%, respectively, p=0.001). After multivariable Cox regression analyses, no differences in all-cause death and the composite end-point were seen between the three groups. HF hospitalization and cardiovascular death were not statistically different between patients with HFmrEF and HFrEF. At 1-year follow-up, 62% of patients with HFmrEF had LVEF measured: 24% had LVEF<40%, 43% maintained LVEF 40-49% and 33% had LVEF>50%. While change in LVEF as continuous variable was not associated with better outcomes, those patients who evolved from HFmrEF to HFpEF did have a better outcome. Those who remained in the HFmrEF and HFrEF groups had higher all-cause mortality after adjustment for age, sex and baseline LVEF (HR 1.96 (95% CI 1.08-3.54, p=0.027 and HR 2.01 (95% CI 1.04-3.86, p=0.037), respectively).

Conclusions: Patients with HFmrEF have a clinical profile in-between HFpEF and HFrEF, without differences in all-cause mortality and the composite end-point between

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the three groups. At 1-year, patients with HFmrEF exhibited the greatest variability in LVEF and this change was associated with survival.

Key words: heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; Heart failure with mid-range ejection fraction; Prognosis; echocardiography; ejection fraction; recovered

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- Cohort study of heart failure (HF) patients followed up at 4 hospitals with a dedicated HF unit, thereby reflecting different clinical practice within guidelines recommendations.
- The hospitals varied from community oriented hospitals to reference centres with transplant and ventricular assist devices programs. The inclusion of hospitals with different levels of complexity determined that baseline characteristics of patients were different among the 4 hospitals, which allows an easier generalization of the results.
- Not all patients had an echocardiogram during follow up, which might have resulted in a bias and affected the results.

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FUNDING:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

DATA SHARING STATEMENT:

Additional unpublished data might be available to those completing the request for research upon acceptance by the GICCAT group.

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INTRODUCTION:

Despite the improvement in knowledge and treatment of heart failure (HF) in the last decades, HF is still a prevalent disease with a bad prognosis [1] and to which considerable healthcare resources are dedicated [2]. Much of the research to date has focused on patients with HF and reduced ejection fraction (HFrEF) and so far pharmacological and invasive treatments have only shown to be useful in this group of patients [3]. Furthermore, definition of HF with preserved ejection fraction (HFpEF) varies widely in registries and in randomized control trials (from left ventricular ejection fraction (LVEF) >40% to > 55%) [4] and hence a grey zone of patients with LVEF ranging 40 to 50% has hardly been studied. For this reason, the last 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF included this new mid-range group in the classification of HF in order to stimulate research in this subpopulation of patients [3]. Previous studies have shown that patients with HFmrEF have a baseline profile in-between of HFrEF and HFpEF, with some characteristics closer to HFrEF (predominant ischemic aetiology) and others to HFpEF (higher prevalence of women and elderly patients). Moreover, differences in outcomes have also been described between groups. Given the differences in baseline characteristics and prognosis in the 3 groups, some authors suggest that HFmrEF has a phenotype closer to HFpEF [5–8] whereas other authors consider it closer to HFrEF [9–11]. In patients with HFrEF (LVEF<40%) an improvement in LVEF has been associated with better outcomes [12]. Whether this is also true in patients with mid-range EF (HFmrEF) is unknown.

Hence, the aim of this study was to analyse the baseline characteristics and outcome of patients with HFmrEF compared to patients with HFpEF (LVEF>50%) and HFrEF and to analyse the effect of 1-year change in LVEF in patients with HFmrEF on outcome.

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METHODS

Study population

This was a prospective observational study of HF patients followed at 4 university hospitals with a dedicated Heart Failure Unit. Patients were consecutively enrolled from August 2001 to June 2015 and HF was diagnosed following the European Society of Cardiology (ESC) guidelines [3]. Baseline demographic, clinical and echocardiographic data were collected. Patients were classified in three groups according to the new ESC Guidelines for the diagnosis and treatment of acute and chronic HF: HFrEF, HFmrEF and HFpEF [3]. Changes in medical therapy over time were not collected.

Data on 1-year LVEF were also collected when available. Follow up echocardiograms were performed as per each institutional protocol. All patients were followed up at regular intervals. Those who failed to attend the clinic appointment were contacted by telephone and hospital and primary care records were reviewed in order to assess vital status and HF hospitalizations. The main outcome was recorded as death from all causes, HF hospitalization and a composite end-point of all-cause death and HF hospitalization. Cardiovascular (CV) death was also analysed. A death was considered of CV origin if it was caused by HF, sudden death, acute myocardial infarction, stroke, CV procedural, or other CV causes.

The study was approved by the Ethics Committees of the participating hospitals (Hospital del Mar (Parc de Salut Mar, Barcelona), Hospital Universitari Germans Trias i Pujol (Badalona), Hospital de Sant Pau (Barcelona) and Hospital de Bellvitge (L'Hospitalet de Llobregat, PR088/16), and all patients gave written informed consent on the initial visit.

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Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), depending on whether data distribution was normal (assessed by normal Q–Q plots); categorical variables were expressed as percentages. A comparative analysis between variables was carried out using Chi-square test (categorical variables) and Student's t-test or Mann–Whitney U-test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables. P-value adjustment for multiple testing was performed by Tukey (normal-distribution) or Benjamini & Hochberg method (otherwise). Kaplan-Meier survival curves were compared by the log-rank test. Multivariate analysis was performed using Cox proportional hazard regression (Cox) including center as strata. In all analyses involving CV death and HF hospitalization, a competing risks strategy by the Gray method was adopted [13], considering non-CV death as the competing event for CV death, and all-cause death for HF hospitalization. HFrEF was used as the reference category. The analyses were performed with R (version 3.3.2) R: A Language and Environment for Statistical Computing (Vienna, Austria). We considered P-values <0.05 from two-sided tests to indicate statistical significance.

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RESULTS:

Baseline clinical characteristics

Baseline clinical characteristics and treatment were categorized according to LVEF and are summarized in Table 1. Fourteen percent (n=504) of the 3580 patients included in the study had HFmrEF, 62% had HFrEF and 24% HFpEF. In the whole cohort, mean age was 68±13 years, 62% were men and mean LVEF was 38±16%. Baseline characteristics of patients with HFmrEF were in-between those of HFpEF and HFrEF. Use of neurohormonal treatment was higher in patients with HFrEF and HFmrEF, whereas the use of loop diuretics was highest in the HFpEF group. The four cohorts were clinically different (see the Supplementary material online, Table S1, describing the baseline characteristics according to hospital).

Follow-up Events

During a median follow-up of 3.66 (1.69-6.04) years, all-cause death, HF hospitalization and the composite end-point were 47%, 35% and 59%, respectively (Table 2). The cause of death was CV in 24.7% of patients, without differences in the three groups (overall p=0.068). Outcomes were worse in HFpEF, without differences between HFrEF and HFmrEF (Figure 1). In multivariable Cox regression analyses, no differences in all-cause death and composite end-point were seen between the three groups. HF hospitalization and CV death were not statistically different between patients with HFmrEF and HFrEF, although a tendency (p=0.068) towards a lower CV mortality in HFmrEF was observed (Table 3). On the other hand, HFpEF patients had significantly higher HF hospitalization and lower CV death (Table 3).

Changes in LVEF

Flow-chart of patients according to the change of LVEF is depicted in Figure 2. Of the 1971 patients with HFrEF alive at 1 year, 67% had an echocardiogram performed: 62% still had LVEF<40% and 21% had LVEF 40-50%. In this group, after adjustment for

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age, sex and baseline EF, hazard ratios (HR) for survival for change in LVEF was 0.97 (95% CI 0.96-0.98, p<0.001).

LVEF of patients with HFmrEF (analysed in 61% of the 438 patients alive at 1-year) had the greatest variation: 24% had reduced LVEF, 43% maintained LVEF 40-49% and 33% had LVEF>50%. Figure 3 shows Kaplan-Meier curves for long-term outcome for changes of LVEF in HFmrEF. There were no differences in mortality between patients who remained in HFmrEF group and those who changed to HFrEF, while survival was significantly higher in those patients who evolved to the HFpEF group (p=0.026). Compared with patients whose LVEF improved enough to move to the HFpEF group, those who remained in the HFmrEF and HFrEF had higher all-cause mortality after adjustment for age, sex and baseline LVEF (HR 1.96 (95% CI 1.08-3.54, p=0.027 and HR 2.01 (95% CI 1.04-3.86, p=0.037), respectively). As a continuous variable, however, and after adjustment for age, sex and baseline LVEF, HR for survival for change in LVEF was 0.99 (95% CI 0.96-1.01, p=0.229). Baseline characteristics of patients who evolved to HFpEF were similar to those who remained in HFmrEF or changed to HFrEF, except for a higher proportion of women (38% vs. 23%, p=0.021) and non-ischemic aetiology (61% vs. 38%, p=0.001), higher diastolic blood pressure (76±11 vs. 72±12 mmHg, p=0.009) and eGFR (70±24 vs. 63±27 mL/min, p=0.028) but lower NTproBNP (901 [450-1690] ng/L vs. 1494 [593-4456], p=0.013). Baseline LVEF was higher (44±3% vs. 42±2%, p<0.001). Interestingly, treatment was similar in both groups, with a high use of beta blockers (95.5% vs. 92.3%, p=0.470), ACEI/ARB (83% vs. 83%, p=1.0) and MRA (40.9% vs. 51.9%, p=0.117). See the Supplementary material online, Table S2, for comparison among the groups.

Finally, among patients with HFpEF alive at one year, only 288 (40%) had LVEF measured at 1 year follow-up, and the majority (85%) of them still had LVEF >50%. After adjustment for age, sex and baseline EF, HR for survival for change in LVEF in this group was 0.99 (95% CI 0.97-1.01, p=0.283).

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Interestingly, at 1-year follow-up, 22.9% of patients were in the HFmrEF category, irrespective of their initial LVEF.

DISCUSSION:

Patients with HFmrEF are a small group in the spectrum of HF patients and their clinical characteristics did not allow differentiating them from HFpEF or HFrEF patients. Moreover, all-cause mortality was not different from that of HFpEF or HFrEF. CV mortality, however, tended to be lower in HFmrEF patients than in HFrEF patients. Interestingly, change in 1-year LVEF in this group was broader (24% had a decrease in LVEF and 33% had LVEF>50%). While change in LVEF fraction as continuous variable was not associated with better outcomes, those patients who evolve from HFmrEF to HFpEF actually did have a better outcome.

Baseline clinical characteristics

Prevalence of HFmrEF in our study was 14%, similar to other studies carried out in hospitalized (prevalence between 13-26%) [5–7,14,15] and ambulatory (9-21%) [9–11,16–18] HF patients. Consistent with other studies, clinical characteristics of patients with HFmrEF did not allow for a clear clinical differentiation of this group. Age and prevalence of women were higher in HFmrEF than in HFrEF but lower than in HFpEF. This finding is consistent across different studies [5,7,8,10,14,16–19]. Some co-morbidities such as diabetes mellitus, dyslipidaemia and COPD were not different between the three groups. In patients with HFmrEF the presence of anaemia, chronic kidney disease and NYHA class III-IV was similar to those with HFrEF but was lower than in those with HFpEF. Interestingly, NTproBNP was not different between HFmrEF and HFpEF but was lower than in HFrEF. Aetiology of HF was also different between the three groups, with a predominant ischemic cause in HFrEF and HFmrEF and hypertensive in HFpEF. Similar results have been described in other studies, and, although some differences

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can be found in the distribution of comorbidities among studies [5–10,14,16,17,19,20], the overall perception is that it is not possible to identify a clear pattern of clinical characteristics that defines HFmrEF, but differences in aetiology, sex and age would point more to a patient with HFrEF.

Follow-up Events

Given the differences in baseline characteristics and prognosis in the 3 groups, some authors suggest that HFmrEF has a phenotype closer to HFpEF [5–8] whereas other authors consider it closer to HFrEF [9–11]. All-cause mortality and HF hospitalization were similar in HFrEF and HFmrEF (45.8% vs 43.8%, p=0.448) but were lower than in HFpEF (52.6%, overall p=0.002). However, in multivariable Cox regression analyses with competing risk, HFpEF performed worse than those with HFmrEF and HFpEF, relative to HF hospitalization but had lower CV mortality. Whilst some studies have shown no differences in outcomes among the three groups [5–7,10,14], other authors have found different results, with a higher mortality in HFmrEF compared to HFpEF in ambulatory HF patients [9] and, contrary to our results, a higher HF hospitalization in HFrEF compared to HFmrEF and HFpEF [8]. Interestingly, we found similar all-cause death between HFrEF and HFmrEF patients, but a trend towards lower CV mortality in the latter group.

Changes in LVEF

At 1-year follow-up, LVEF of patients with HFmrEF had the greatest variation: 24% had reduced LVEF, 43% maintained LVEF 40-49% and 33% had LVEF>50%. Remarkably, in this group, change in LVEF as continuous variable was not associated with survival but when the improvement in LVEF was enough to move the patient from HFmrEF to HFpEF, survival improved significantly. Women and non-ischemic aetiology were more frequent in patients who moved to HFpEF and that has been shown in other studies [21]. Although treatment has been associated with improvement in LVEF [22–24] we did not see

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any difference in treatment between patients who moved to HFpEF and those who remained in HFmrEF or went to HFrEF. However, this lack of difference might be explained by the high use of Class I medications in our population.

The apparent paradox of absence of a clear difference in long-term prognosis in patients according to the three groups of LVEF can be plausibly disentangled. On the one hand, LVEF measured by echocardiography is an imperfect measure to determine left ventricular systolic function as it only captures one part of the whole biomechanics of cardiac function and exhibits important variability [25]. Moreover, impairment of left ventricular systolic function is also present in patients with HFpEF, even though their LVEF might be normal [26]. On the other hand, cut-offs used to define the three groups (HFrEF, HFmrEF and HFpEF) are arbitrary [3]. Finally, LVEF is a dynamic measure that can vary with treatment [22,23] and during follow-up [17,23]. In the present study, 437 patients had HFmrEF according to the echocardiogram at 1-year follow up. This represents an increase from 14% at baseline to 22.9% at 1-year follow-up. Previous studies have shown that depending on the cut-off used (LVEF 40% vs. 50%), up to 50% of patients with HFpEF were patients with previously reduced LVEF [27,28] and patients with recovered LVEF had a better prognosis compared to those with preserved or reduced LVEF [20,21,24,27–29] and with those who did not improve LVEF [12]. Although it was less frequent, patients with HFpEF also showed variability in LVEF during follow-up (only 15% of HFpEF patients had LVEF<50% at 1-year follow-up in our study). Dunlay et al. showed that among HFpEF patients, 21.1% had an EF<50% around 1 year after diagnosis, and this increased to 32.5% in those with an echo performed from 4 to 6 years after diagnosis [24], and similar results were seen in other studies [18,22]. In the present study, change in LVEF in HFpEF was not independently associated with all-cause mortality. In HFmrEF, patients whose LVEF improved enough to move to HFpEF, outcome was better but when LVEF did not move or worsened, prognosis was

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worse, consistently with other studies that showed that irrespective of baseline group, the transition to HFrEF was associated with increased all-cause mortality [18].

Taken together, the results of the present and previous studies show that the classification of patients in HF with preserved, mid-ranged and reduced LVEF is not static. In other words, many patients with HFmrEF might be either recovered HFrEF patients or, probably to a lesser extent, patients with worsened HFpEF and this fact might explain the difficulty in clinically characterizing them properly and might explain the lack of differences found in all-cause mortality between the three groups. Irrespective of the limitations LVEF might have to classify patients with different prognosis, baseline echocardiogram has the crucial role to identify patients in whom disease modifying treatment are useful to improve prognosis. Whether baseline LVEF or follow-up LVEF should be used to classify patients remains unclear.

Limitations:

Follow-up echocardiograms were not done at pre-specified intervals in all patients. This might have been a source of bias because the decision to perform a follow-up echocardiogram may have been influenced by clinical status, age and baseline LVEF. Table 3 in the Supplemental material shows the differences between patients who survived 1 year with and without an echocardiogram done at follow up. We have added a Table in the Supplemental material showing the differences between patients with and without an echocardiogram done at follow up. Patients without an echocardiogram at follow-up were older and had more comorbidity. This group of patients are more frequently not studied with echocardiogram [24]. It might have been thought that no benefit would be derived from serial echocardiograms due to poor predicted outcome or presumed HFpEF. Conversely, patients with 1-year follow-up echocardiogram had lower baseline LVEF and were more frequently on optimal medical therapy. In this group of patients, some recovery of LVEF may be expected and this may influence subsequent decisions regarding ICD or CRT suitability, therefore serial

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echocardiograms are more often done. Finally, Dunlay et al report that their patients had a median of 2 echocardiograms during follow up and mean time from initial to final EF measurement was around 3 years but these authors did not report how many patients had an echocardiogram done at 1-year follow up [24]. In another study, 43% of patients with a primary hospital discharge diagnosis for HF did not have 2 or more LVEF tests ≥ 30 days apart during the study period [22]. Hence, considering that in the present study two thirds of patients had an echocardiogram done at 1-year follow up, we think that results are consistent with common clinical practice.

NT-proBNP was missing in 25% of our patients and therefore this biomarker was not included in the multivariable analysis. Consistently with our results, van Veldhuisen et al. showed that BNP levels were lower in patients with HFpEF than in HFrEF. For a given BNP level, that study showed that the prognosis in patients with HFpEF was similar than those with reduced LVEF [30].

Finally, the baseline characteristics of the patients included in the 4 hospitals are remarkably different. Although that may be seen as a limitation, the inclusion of different type of HF patients allowed us to better characterize this population, combining patients followed up in centres with different degree of specialization (advanced HF centres and community oriented hospitals), thus including patients that would have been lost if only centres with similar characteristics were analysed.

CONCLUSIONS:

Patients with HFmrEF have a clinical profile in between HFpEF and HFrEF and there were no differences in all-cause mortality and the composite end-point between the three groups. At 1-year follow-up, patients with HFmrEF had the greatest variability (up and down) in LVEF but change in LVEF was not associated with survival, except when patients actually evolve to HFpEF. The classification of patients in HF with preserved, mid-ranged and reduced LVEF is not static and thus, the only reason to classify

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patients according to their LVEF would be to identify patients in whom disease-modifying therapies are useful to improve prognosis.

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FIGURE LEGENDS:

Figure 1: Kaplan-Meier curves for long-term outcome divided by LVEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence; C, composite end-point cumulative survival).

Figure 2: Flow-chart of patients according to the change of LVEF

Figure 3: Kaplan-Meier curves for long-term outcome for changes of LVEF in the HFrmEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence).

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Table 1 Baseline clinical characteristics and treatment categorized according to LVEF.

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	All N=3580	HFrEF N=2232 (62%)	HFmrEF N=504 (14%)	HFpEF N=844 (24%)	P value *	P value **	P value ***	N
Male	2397 (67.0)	1689 (75.7)	337 (66.9)	371 (44.0)	<0.001	<0.001	<0.001	3580
Age	68.2±12.7	66.2±12.5	68.1±12.9	73.5±11.4	<0.001	0.003	<0.001	3580
LVEF	38.3±16.0	28.0±6.9	43.5±2.9	62.5± 8.3	<0.001	<0.001	<0.001	3580
Etiology:					<0.001	<0.001	<0.001	3579
ischemic	1600 (44.7)	1174 (52.6)	261 (51.8)	165 (19.5)				
dilated	552 (15.4)	450 (20.2)	58 (11.5)	44 (5.21)				
hypertensive	592 (16.5)	169 (7.58)	72 (14.3)	351 (41.6)				
valvular	321 (8.97)	131 (5.87)	45 (8.93)	145 (17.2)				
other	514 (14.4)	307 (13.8)	68 (13.5)	139 (16.5)				
Heart rate	72.7± 14.8	72.8±14.9	70.8± 14.3	73.8±14.6	0.001	0.005	<0.001	3577
Hypertension	2485 (69.4)	1434 (64.2)	366 (72.6)	685 (81.2)	<0.001	<0.001	<0.001	3580
Diabetes mellitus	1547 (43.2)	956 (42.8)	210 (41.7)	381 (45.1)	0.386	0.669	0.235	3580
COPD	721 (20.1)	427 (19.1)	103 (20.4)	191 (22.6)	0.096	0.544	0.381	3580
Dyslipidemia	1843 (51.5)	1158 (51.9)	263 (52.2)	422 (50.0)	0.611	0.942	0.472	3580
Atrial fibrillation	999 (27.9)	435 (19.5)	158 (31.3)	406 (48.2)	<0.001	<0.001	<0.001	3579
BMI, Kg/m2	27.8±5.30	27.3±4.93	28.2±5.30	28.9±6.01	<0.001	<0.001	0.045	3528
Sodium, mmol/L	139±4.33	139±4.67	140±3.50	140± 3.63	<0.001	<0.001	0.730	3556
Anemia	1231 (34.9)	656(29.9)	184(37.1)	391(46.8)	<0.001	0.002	0.001	3580
NT-proBNP, ng/L	1638 (697;3937)	1898 (769;4465)	1484 (532;3866)	1320 (635;2818)	<0.001	<0.001	0.518	2705
eGFR, mL/min/1.73m2	60.4±25.4	62.4±25.4	60.4±26.5	55.2±23.8	<0.001	0.125	<0.001	3562
NYHA class III–IV	1293 (36.1)	746 (33.4)	172 (34.1)	375 (44.4)	<0.001	0.808	<0.001	3579
Treatment:								
ACEI or ARB	2992 (83.9)	1992 (89.5)	412 (82.1)	588 (70.1)	<0.001	<0.001	<0.001	3567
Beta-blockers	3094 (86.4)	2040 (91.4)	448 (88.9)	606 (71.8)	<0.001	0.092	<0.001	3580

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MRA	1890 (52.8)	1447 (64.8)	219 (43.5)	224 (26.5)	<0.001	<0.001	<0.001	3580
Loop diuretics	3189 (89.1)	2002 (89.7)	423 (83.9)	764 (90.5)	<0.001	<0.001	<0.001	3580
Digoxin	959 (27.7)	675 (30.8)	106 (21.7)	178 (22.5)	<0.001	<0.001	0.788	3467
ICD	396 (11.1)	359 (16.1)	26 (5.16)	11 (1.31)	<0.001	<0.001	<0.001	3578
CRT	234 (6.54)	213 (9.54)	16 (3.17)	5 (0.59)	<0.001	<0.001	0.001	3580
Anticoagulants	1684 (47.0)	969 (43.4)	239 (47.4)	476 (56.4)	<0.001	0.113	0.002	3580

Data are mean ± standard deviation, median (interquartile range) or n (%). *P-values for the comparison of all three groups (null hypothesis: all three groups have the same characteristics). **P-value only applies to the comparison of HFrEF vs. HFmrEF. ***P-value only applies to the comparison of HFpEF vs. HFmrEF. Anemia was defined as a hemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide. HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction; HFpEF, heart failure with preserved left ventricle ejection fraction.

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Table 2: Mortality, cause of death and heart failure hospitalization during follow-up

	All N=3580	HFrEF N=2232 (62%)	HFmrEF N=504 (14%)	HFpEF N=844 (24%)	P value *	P value **	P value ***	N
All-cause death	1688 (47.2)	1023 (45.8)	221 (43.8)	444 (52.6)	0.001	0.448	0.003	3580
Cause of death					<0.001	0.164	0.011	3580
HF	458 (12.8)	269 (12.1)	58 (11.5)	131 (15.5)				
Sudden death	126 (3.52)	101 (4.53)	13 (2.58)	12 (1.42)				
Other cardiovascular	196 (5.47)	122 (5.47)	29 (5.75)	45 (5.33)				
Non cardiovascular	500 (14.0)	265 (11.9)	72 (14.3)	163 (19.3)				
Unknown	408 (11.4)	266 (11.9)	49 (9.7)	93 (11.0)				
HF hospitalization	1259 (35.2)	724 (32.4)	157 (31.2)	378 (44.8)	<0.001	0.613	<0.001	3580
Composite end-point	2113 (59.0)	1277 (57.2)	272 (54.0)	564 (66.8)	<0.001	0.201	<0.001	3580

Data are n (%). *P-values for the comparison of all three groups (null hypothesis: all three groups have the same characteristics). **P-value only applies to the comparison of HFrEF vs. HFmrEF. ***P-value only applies to the comparison of HFpEF vs. HFmrEF.

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Table 3: Multivariable Cox regression analyses with hospital as strata for all-cause death, heart failure hospitalization, composite end-point and cardiovascular death

	All-cause death		HF hospitalization		Composite end-point (All-cause death + HF hospitalization)		CV death	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
HFrEF	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
HFmrEF	0.93 (0.80-1.08)	0.338	1.00 (0.84-1.20)	0.98	0.94 (0.82-1.07)	0.358	0.80 (0.64-1.01)	0.061
HFpEF	0.93 (0.81-1.06)	0.265	1.18 (1.02-1.38)	0.032	0.95 (0.84-1.06)	0.362	0.75 (0.62-0.92)	0.006
Female	0.75 (0.67-0.84)	<0.001	-		0.85 (0.77-0.94)	0.002	0.75 (0.64-0.88)	<0.001
Age	1.03 (1.03-1.04)	<0.001	-		1.02 (1.02-1.03)	<0.001	1.03 (1.02-1.04)	<0.001
Heart rate	1.00 (1.00-1.01)	0.013	-		1.00 (1.00-1.01)	0.008	-	
DBP	0.99 (0.99-1.00)	0.002	0.99 (0.99-1.0)	0.044	0.99 (0.99-1.00)	0.001	0.99 (0.98-0.99)	<0.001
Dyslipidemia	0.86 (0.78-0.96)	0.004	1.25 (1.10-1.41)	<0.001	-		-	
DM	1.30 (1.17-1.44)	<0.001	1.22 (1.08-1.37)	0.002	1.27 (1.16-1.39)	<0.001	1.27 (1.11-1.47)	<0.001
COPD	1.32 (1.17-1.48)	<0.001	1.27 (1.10-1.47)	<0.001	1.30 (1.17-1.45)	<0.001	-	
BMI	0.98 (0.97-0.99)	<0.001	-		-		-	
Sodium	-		-		-		0.99 (0.97-1.00)	0.024
Hemoglobin	0.93 (0.90-0.96)	<0.001	0.90 (0.87-0.93)	<0.001	0.91 (0.89-0.93)	<0.001	0.93 (0.89-0.97)	0.001
eGFR	0.99 (0.99-1.00)	<0.001	0.99 (0.99-0.99)	<0.001	0.99 (0.99-1.00)	<0.001	0.99 (0.99-0.99)	<0.001
NYHA class III-IV	1.62 (1.46-1.80)	<0.001	1.34 (1.18-1.51)	<0.001	1.54 (1.40-1.69)	<0.001	1.61 (1.39-1.86)	<0.001
ACEI or ARB	0.70 (0.62-0.81)	<0.001	-		0.74 (0.65-0.83)	<0.001	-	
Beta-blockers	0.60 (0.53-0.69)	<0.001	-		0.70 (0.62-0.79)	<0.001	0.60 (0.49-	<0.001

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							0.72)	
Loop diuretics	1.28 (1.04-1.57)	0.020	2.97 (2.18-4.06)	<0.001	1.61 (1.33-1.94)	<0.001	1.88 (1.32-2.67)	<0.001
CRT	0.70 (0.55-0.89)	0.003	-		-		-	
ICD	-		-		-		0.77 (0.60-0.98)	0.032
MRA	-		1.18 (1.03-1.34)	0.014	-		-	
Digoxin	-		1.48 (1.29-1.69)	<0.001	-		1.26 (1.08-1.47)	0.004
Anticoagulants	-		-		-		-	
Hypertension	-		-		1.12 (1.01-1.25)	0.033	-	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate (CKD-EPI equation); MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction ; HFpEF, heart failure with preserved left ventricle ejection fraction.

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AUTHOR'S CONTRIBUTION:

All authors fulfill the ICMJE criteria for authorship:

- Substantial contributions to the conception or design of the work (N.F., J.C.C., J.L., A.B.G., J.V., S.P.), or the acquisition (N.F., E.R., J.G.C., M.A., E.S.G., C.S.E., P.M., S.R., C.E., S.M.), analysis (N.F., J.C.C., J.L., J.V., S.P.) or interpretation of data (N.F., J.C.C., J.L., A.B.G., J.V., S.P., E.R., J.G.C., M.A., E.S.G., C.S.E., P.M., S.R., C.E., S.M.), analysis (N.F., J.C.C., J.L., J.V., S.P.).
- Drafting the work or revising it critically for important intellectual content (all authors).
- Final approval of the version published (all authors).
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (all authors).

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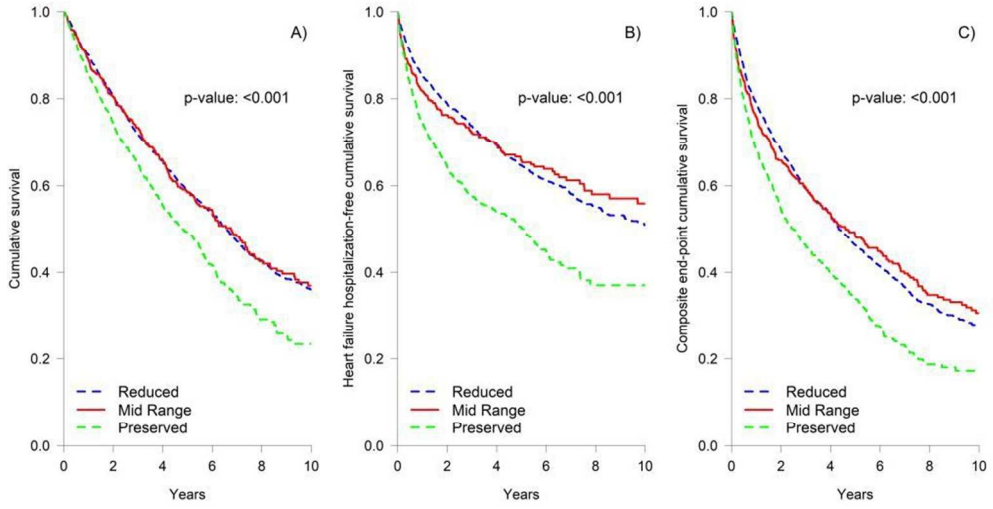

Figure 1: Kaplan-Meier curves for long-term outcome divided by LVEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence; C, composite end-point cumulative survival).

86x48mm (300 x 300 DPI)

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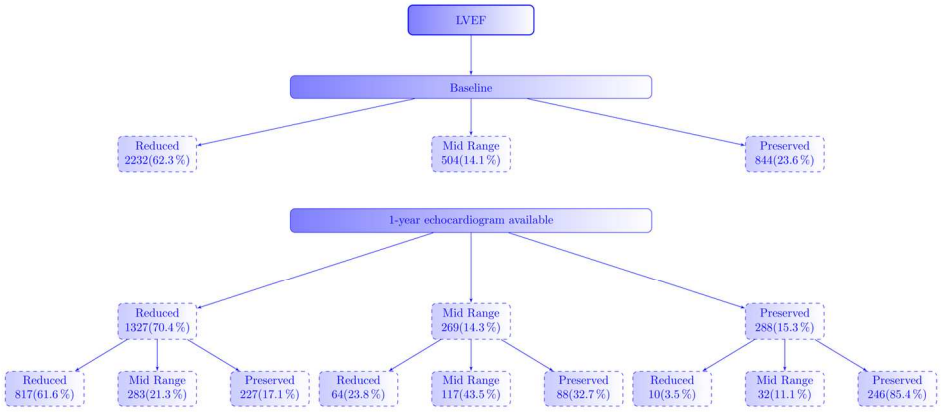

Figure 2: Flow-chart of patients according to the change of LVEF

140x66mm (300 x 300 DPI)

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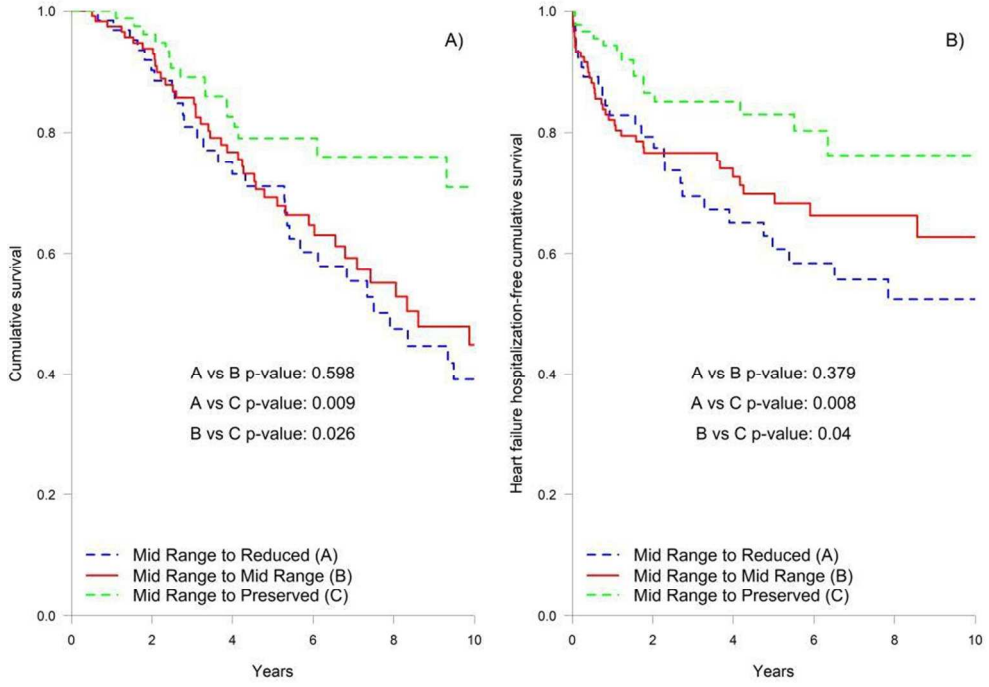

Figure 3: Kaplan-Meier curves for long-term outcome for changes of LVEF in the HFrmEF (A, cumulative survival; B, HF hospitalization-free cumulative incidence).

86x65mm (300 x 300 DPI)

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SUPPLEMENTAL MATERIAL

Table 1: Baseline clinical characteristics for the four hospital cohorts

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	All N=3580	Mar N=1062	H St Pau N=464	Can Ruti N=1835	Bellvitge N=219	P value	N
Male	2232 (62.3)	603 (56.8)	315 (67.9)	1310 (71.4)	169 (77.2)	<0.001	3580
Age	68.2 (12.7)	72.4 (11.3)	67.6 (13.5)	66.8 (12.6)	61.0 (12.1)	<0.001	3580
LVEF	38.3 (16.0)	44.8 (17.0)	42.8 (17.0)	34.2 (13.8)	31.9 (11.7)	<0.001	3580
HF group according to LVEF:						<0.001	3580
HFrEF	2232 (62.3)	471 (44.4)	237 (51.1)	1339 (73.0)	185 (84.5)		
HFmrEF	504 (14.1)	158 (14.9)	75 (16.2)	251 (13.7)	20 (9.13)		
HFpEF	844 (23.6%)	433 (40.8)	152 (32.8)	245 (13.4)	14 (6.39)		
Aetiology:						<0.001	3579
ischemic	1600 (44.7)	419 (39.5)	163 (35.1)	928 (50.6)	90 (41.3)		
dilated	552 (15.4)	111 (10.5)	135 (29.1)	241 (13.1)	65 (29.8)		
hypertensive	592 (16.5)	365 (34.4)	50 (10.8)	173 (9.43)	4 (1.83)		
valvular	321 (8.97)	48 (4.52)	77 (16.6)	176 (9.59)	20 (9.17)		
other	514 (14.4)	119 (11.2)	39 (8.41)	317 (17.3)	39 (17.9)		
Heart rate	72.7 (14.8)	74.5 (15.0)	73.4 (14.3)	71.8 (14.8)	70.5 (13.9)	<0.001	3577
Hypertension	2485 (69.4)	857 (80.7)	351 (75.6)	1153 (62.8)	124 (56.6)	<0.001	3580
Diabetes mellitus	1547 (43.2)	503 (47.4)	182 (39.2)	771 (42.0)	91 (41.6)	0.008	3580
COPD	721 (20.1)	238 (22.4)	125 (26.9)	321 (17.5)	37 (16.9)	<0.001	3580
Dyslipidaemia	1843 (51.5)	589 (55.5)	238 (51.3)	918 (50.0)	98 (44.7)	0.007	3580
Atrial fibrillation	999 (27.9)	358	208 (44.8)	389 (21.2)	44 (20.2)	<0.001	3579

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		(33.7)					
BMI, Kg/m2	27.8 (5.30)	28.3 (5.70)	28.4 (5.12)	27.4 (5.09)	26.5 (4.80)	<0.001	3528
Sodium, mmol/L	139 (4.33)	140 (3.49)	140 (3.32)	138 (3.63)	139 (9.96)	<0.001	3556
Anaemia	1104 (31.3)	420 (39.5)	127(27.4)	603 (33.8)	81 (37.0)	<0.001	3526
NT-proBNP, ng/L	1638 (697;3937)	1577 (688;3996)	1618 (753;3701)	1750 (704;4210)	1420 (572;3198)	0.217	2705
eGFR, mL/min/1.73m2	60.4 (25.4)	56.0 (22.5)	60.4 (25.7)	62.2 (26.4)	67.7 (25.2)	<0.001	3562
NYHA class III–IV	1293 (36.1)	452 (42.6)	172 (37.1)	573 (31.2)	96 (44.0)	<0.001	3579
Treatment:							
ACEI or ARB	2992 (83.9)	793 (74.7)	397 (85.6)	1597 (87.0)	205 (99.5)	<0.001	3567
Beta-blockers	3094 (86.4)	922 (86.8)	373 (80.4)	1611 (87.8)	188 (85.8)	0.001	3580
MRA	1890 (52.8)	406 (38.2)	232 (50.0)	1107 (60.3)	145 (66.2)	<0.001	3580
Loop diuretics	3189 (89.1)	959 (90.3)	385 (83.0)	1654 (90.1)	191 (87.2)	<0.001	3580
Digoxin	959 (27.7)	137 (12.9)	24 (6.84)	732 (39.9)	66 (30.1)	<0.001	3467
ICD	396 (11.1)	24 (2.26)	74 (16.0)	232 (12.6)	66 (30.1)	<0.001	3578
CRT	234 (6.54)	11 (1.04)	33 (7.11)	153 (8.34)	37 (16.9)	<0.001	3580
Anticoagulants	1684 (47.0)	504 (47.5)	210 (45.3)	873 (47.6)	97 (44.3)	0.673	3580

Data are mean ± standard deviation, median (interquartile range) or n (%). P-values for the comparison of all four groups (null hypothesis: all three groups have the same characteristics). Anaemia was defined as a haemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass

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index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide. HFrEF, heart failure with reduced left ventricle ejection fraction; HFmrEF, heart failure with mid-range left ventricle ejection fraction; HFpEF, heart failure with preserved left ventricle ejection fraction.

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Table 2: Baseline clinical characteristics of patients with HFmrEF according to the change of HF category at 1-year follow up.

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	All N=269	Mid-range to reduced N=64	Mid-range to mid-range N=117	Mid-range to preserved N=88	P value overall	N
Male	197 (72.1)	52 (81.2)	87 (74.4)	55 (62.5)	0.030	269
Age	65.2 (12.2)	67.0 (10.6)	64.4 (12.5)	64.8 (12.9)	0.380	269
LVEF	42.9 (2.72)	41.9 (2.28)	42.8 (2.51)	44.0 (2.96)	<0.001	269
Aetiology:					0.005	269
ischemic	144 (53.5)	44 (68.8)	67 (57.3)	33 (37.5)		
dilated	36 (13.4)	5 (7.8)	18 (15.4)	13 (14.8)		
hypertensive	26 (9.7)	5 (7.8)	9 (7.7)	12 (13.6)		
valvular	24 (8.9)	6 (9.4)	10 (8.6)	8 (9.1)		
other	39 (14.5)	4 (6.3)	13 (11.1)	22 (25.0)		
Heart rate	70.0 (13.9)	69.5 (14.3)	69.5 (13.8)	71.1 (13.9)	0.695	269
Hypertension	180 (66.9)	50 (78.1)	76 (65.0)	54 (61.4)	0.080	269
Diabetes mellitus	112 (41.6)	26 (40.6)	50 (42.7)	36 (40.9)	0.949	269
COPD	43 (16.0)	8 (12.5)	19 (16.2)	16 (18.2)	0.637	269
Dyslipidaemia	156 (58.0)	41 (64.1)	67 (57.3)	48 (54.5)	0.491	269
Atrial fibrillation	81 (30.1)	18 (28.1)	31 (26.5)	32 (36.4)	0.289	269
BMI, Kg/m2	28.4 (5.1)	27.9 (5.1)	28.2 (4.7)	29.1 (5.7)	0.323	263
Sodium, mmol/L	140 (3.2)	140 (3.4)	140 (3.2)	140 (3.2)	0.887	265
Anaemia	84 (31.8)	24 (38.1)	35 (30.4)	25 (29.1)	0.462	264
NT-proBNP, ng/L	1037 [502;3304]	2186 [933;4456]	1000 [482;4287]	901 [450;1690]	0.005	190
eGFR, mL/min/1.73m2	65.3 (26.2)	60.7 (27.0)	64.2 (27.4)	70.2 (23.5)	0.078	264
NYHA class III–IV	74 (27.5)	18 (28.1)	31 (26.5)	25 (28.4)	0.947	269
Treatment:						
ACEI or ARB	224 (83.3)	50 (78.1)	101 (86.3)	73 (83.0)	0.367	269
Beta-blockers	251 (93.3)	56 (87.5)	111 (94.9)	84 (95.5)	0.135	269

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MRA	130 (48.3)	40 (62.5)	54 (46.2)	36 (40.9)	0.026	269
Loop diuretics	218 (81.0)	53 (82.8)	96 (82.1)	69 (78.4)	0.739	269
Digoxin	65 (24.9)	17 (27.0)	25 (22.3)	23 (26.7)	0.704	261
ICD	17 (6.3)	10 (15.6)	5 (4.3)	2 (2.3)	0.003	269
CRT	11 (4.1)	4 (6.3)	6 (5.1)	1 (1.1)	0.212	269
Anticoagulants	138 (51.3)	27 (42.2)	64 (54.7)	47 (53.4)	0.243	269

Data are mean ± standard deviation, median (interquartile range) or n (%). P-values for the comparison of all four groups (null hypothesis: all three groups have the same characteristics). Anaemia was defined as a haemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Table 3: Baseline clinical characteristics of patients with an echocardiogram performed at 1-year follow up compared to those without.

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	All N=3580	No follow-up echocardiogram N=1696	Follow-up echocardiogram N=1884	P value overall	N
Male	2397 (67.0%)	1062 (62.6%)	1335 (70.9%)	<0.001	3580
Age	68.2 (12.7)	71.1 (12.5)	65.6 (12.2)	<0.001	3580
LVEF	38.3 (16.0)	41.7 (17.3)	35.3 (14.0)	<0.001	3580
Aetiology:				<0.001	3579
ischemic	1600 (44.7%)	729 (43.0%)	871 (46.3%)		
dilated	552 (15.4%)	203 (12.0%)	349 (18.5%)		
hypertensive	592 (16.5%)	390 (23.0%)	202 (10.7%)		
valvular	321 (8.97%)	150 (8.84%)	171 (9.08%)		
other	514 (14.4%)	224 (13.2%)	290 (15.4%)		
Hypertension	2485 (69.4%)	1250 (73.7%)	1235 (65.6%)	<0.001	3580
Diabetes mellitus	1547 (43.2%)	785 (46.3%)	762 (40.4%)	<0.001	3580
COPD	721 (20.1%)	395 (23.3%)	326 (17.3%)	<0.001	3580
Atrial fibrillation	999 (27.9%)	532 (31.4%)	467 (24.8%)	<0.001	3579
BMI, Kg/m2	27.8 (5.30)	27.8 (5.52)	27.7 (5.09)	0.683	3528
Sodium, mmol/L	139 (4.33)	139 (3.80)	139 (4.75)	0.033	3556
Anaemia	1231 (34.9%)	686 (41.3%)	545 (29.3%)	<0.001	3526
NT-proBNP, ng/L	1638 [697;3937]	1790 [716;4432]	1502 [668;3392]	0.001	2705
eGFR, mL/min/1.73m2	60.4 (25.4)	56.0 (25.1)	64.5 (24.9)	<0.001	3562
NYHA class III–IV	1293 (36.1%)	745 (44.0%)	548 (29.1%)	<0.001	3579
Treatment:					
ACEI or ARB	2992 (83.9%)	1316 (78.0%)	1676 (89.2%)	<0.001	3567
Beta-blockers	3094 (86.4%)	1379 (81.3%)	1715 (91.0%)	<0.001	3580

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MRA	1890 (52.8%)	744 (43.9%)	1146 (60.8%)	<0.001	3580
Loop diuretics	3189 (89.1%)	1513 (89.2%)	1676 (89.0%)	0.852	3580
Digoxin	959 (27.7%)	394 (24.0%)	565 (31.0%)	<0.001	3467
ICD	396 (11.1%)	109 (6.43%)	287 (15.2%)	<0.001	3578
CRT	234 (6.54%)	63 (3.71%)	171 (9.08%)	<0.001	3580
Anticoagulants	1684 (47.0%)	801 (47.2%)	883 (46.9%)	0.855	3580
1-year mortality	400 (11.2%)	364 (21.5%)	36 (1.91%)	<0.001	3580
Baseline Ejection Fraction:				<0.001	3580
Reduced	2232 (62.3%)	905 (53.4%)	1327 (70.4%)		
Mid-Range	504 (14.1%)	235 (13.9%)	269 (14.3%)		
Preserved	844 (23.6%)	556 (32.8%)	288 (15.3%)		

Data are mean ± standard deviation, median (interquartile range) or n (%). P-values for the comparison of all four groups (null hypothesis: all three groups have the same characteristics). Anaemia was defined as a haemoglobin < 12 g/dL, ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (CKD-EPI equation); ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – Page 1 and 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported – Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses – Page 7
Methods		
Study design	4	Present key elements of study design early in the paper – Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – Page 8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up – Page 8 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable – Pages 8 and 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why – Page 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Page 9
		(*b*) Describe any methods used to examine subgroups and interactions - Page 9
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed – Page 9 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage – Page 8, 15
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Page 10, 23-25
		(b) Indicate number of participants with missing data for each variable of interest - Page 23-25
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) – Page 10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time – Page 10, 26-28
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – Page 26-28
		(*b*) Report category boundaries when continuous variables were categorized – Pages 10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – Page 10-12
Discussion		
Key results	18	Summarise key results with reference to study objectives – Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias – Page 15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results - Page 12-16
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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