Differences in clinical outcomes, healthcare resource utilization and costs in heart failure patients according to left ventricular ejection fraction

Running title: ***Left ventricular ejection fraction outcome differences in heart failure patients***

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ABSTRACT

Aims. The impact of left ventricular ejection fraction (LVEF) on healthcare resource utilization (HCRU) and cost in HF patients is not well known. We aimed to compare outcomes, HCRUs and costs according to LVEF groups.

Methods. Retrospective, observational study on all patients with emergency department (ED) visit or admission to Hospital Universitario 12 de Octubre, Madrid, Spain, during year 2018 with a primary diagnosis code of HF (ICPC-2 in ED or ICD-10-CM in hospital) according to LVEF. In-hospital new onset HF or unavailable LVEF were excluded. Thirty-day, and 1-year clinical outcomes, HCRU and costs were compared.

Results. From 1287 patients with primary HF diagnosis, 3 died in the ED and 365 (28.4%) were discharged home (ED group), and 919 (71.4%) were hospitalized. In total, 190 patients (14.7%) had reduced LVEF (HFrEF), 146 (11.4%) mildly reduced LVEF (HFmrEF) and 951 (73.9%) preserved LVEF (HFpEF). Mean age was 80.1±10.7 years; 57.1% were female. Median patient-year costs were €1,889 (259-6,269) in the ED group and €5,008 (2,747-9,589) in the hospital group ($p<0.001$). HFrEF patients showed no significantly worse 1-year outcomes with the exception of higher hospitalization rates in the ED group but showed higher median costs in the ED group (€4,763 [interquartile range, 2,076-17,155] vs €3,900 [590-8,013) for HFmrEF vs €812 [259-5,486] for HFpEF), and hospital group (€6,321 [3,335-796] vs €6,170 [3,189-10,484] vs €4,636 [2,609-8,977], respectively) (both $p<0.001$).

Conclusion. HF has a significant impact on outcomes, HCRU and costs across the whole spectrum of LVEFs with differences among LVEF groups but most notably by initial management (initially discharged from ED or hospitalized).

INTRODUCTION

Heart failure (HF) is a major health problem, with a prevalence of 1-3% in the general population worldwide, which will increase in the next decades.[1,2] The global impact of HF on healthcare is also growing, consuming 3-8% of healthcare spending in developed countries.[3–5]

HF is a heterogeneous syndrome in which the common denominator is cardiac dysfunction.[6] The 2021 clinical guidelines for the diagnosis and treatment of HF of the European Society of Cardiology differentiates three types of HF according to left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF), with mildly reduced ejection fraction (HFmrEF), and with preserved ejection fraction (HFpEF).[7] Despite their epidemiological, pathophysiological, and prognostic differences, the impact of LVEF ranges on the need for healthcare resources and related costs is not well defined. A few studies have addressed this topic but contradictory results have been reported.[8–12] The aim of our study is to compare outcomes, healthcare resource utilization and related costs in patients with a primary diagnosis of HF and different LVEF ranges who needed clinical attention in a hospital facility at least once, either in the emergency department (ED) alone or with hospitalization.

METHODS

This is an observational, retrospective, cohort study based on administrative and electronic health records (EHR)-derived data.

Patients. All patients aged 18 years or older who had at least one visit to the adult emergency department (ED) and/or were admitted to the Hospital Universitario 12 de Octubre, Madrid, Spain, during calendar year 2018 (January 1st, 2018, to December 31st, 2018) and had a main diagnosis of HF were included. This information was obtained directly from the hospital's ED database and the minimum basic data sets. Patients who developed new onset HF during hospitalization initially for other reason or those with a secondary HF diagnosis at discharge were excluded.[13] Patients without a registered echocardiographic study, unknown LVEF or with unavailable or inconsistent information were excluded. We also excluded patients with primary valvular heart disease, acute coronary syndrome, HF due to systemic diseases (e.g., thyrotoxicosis, hepatic cirrhosis, and end-stage renal failure), heart and kidney transplant recipients and patients with prior left ventricular assist device.

Heart failure diagnosis. Diagnoses were obtained either from 1) the ED database (International Classification of Primary Care, 2nd edition, K77 code) or 2) the Admission and Emergency Minimum Basic Data Sets (Inclusion criterion: International Classification of Diseases, Tenth Revision, Clinical Modification codes I11.0*, I13.0*, I13.2* and I50*).

Patient subgroups. We differentiated three groups of patients with HF according to measured LVEF: 1) HFrEF, if LVEF was ≤40%; 2) HFpEF, if LVEF≥50%, and 3) HFmrEF if LVEF was 41-49%.

Outcomes and healthcare resource use. Information on clinical outcomes and use of healthcare resources was obtained by analysis of the hospital's patient management information system, which integrates electronic health record and most administrative data. Mortality and healthcare resource utilization after discharge were

registered during the following year after the ED or hospital discharge through the online Madrid regional population information system (CIBELES) that gives information on vital status, recording (all-cause) mortality at a population level. This database is part of the Madrid regional healthcare service (*Servicio Regional de Salud de Madrid, SERMAS*) information system.

ED visits were considered as any medical attention in the hospital ED regardless of the time spent and the final disposition. Any visit to the hospital ED for any reason after the index ED visit discharge was computed as a re-ED visit. The length of ED stay was calculated as the date of ED discharge or hospital admission minus ED admission date. Hospital stays were computed as any time in the hospital lasting beyond midnight. Length of hospital stay was calculated as the date of discharge minus the admission date in days. Index hospitalization was defined as the first admission registered in the trajectory of the patient related to the first hospital visit (through the ED or not). However, admissions after direct discharges home from the ED were considered hospitalizations rather than rehospitalizations. Readmissions were considered as any hospital stay for any reason after discharge from the index hospitalization. Hospitalizations after an index ED visit with direct discharge home were not recorded as readmissions. Specific cuts were done at 30 days and 1 year after index discharge. Outpatient visits were defined as any scheduled medical or nursing consultation; any day-hospital visit or any cardiac rehabilitation visit (classified each as first or subsequent).

The Clinical Outcomes, HEalthcare REsource utilizatioN, and relaTed costs (COHERENT) model was used for the representation of the mortality-healthcare resource utilization composite outcome, and for cost calculation.[13,14] In brief, this is a

graphical model to evaluate complex composite outcomes built up by developing a hierarchical code system with a mutually exclusive list of potentially relevant clinical situations defined as the patient clinical status (alive or dead) and location (i.e. at home, ED or in hospital), linked to a specific cost calculator, which are computed daily during each defined observation period.[14]

Cost calculation. Cost calculations have been described elsewhere.[16,17] In brief, data provided by the Accountability Department of Hospital Universitario 12 de Octubre was used for reporting costs for clinical situations. This method consists of a full cost system in which the cost of each episode is calculated by the addition of all costs imputable to the patient or the episode (housing, diets, drugs, devices), the unitary costs of each product or activity included in the hospital service catalogue (laboratory analysis, diagnostic and therapeutic interventions, operating room times, postoperative recovery unit stays) and all other costs that cannot be directly imputed to the patient or the episode (residual cost), which are transferred to the clinical episode cost through the indirect imputation criteria. Hospital Universitario 12 de Octubre belongs to the Spanish Network of Hospital Costs (RECH in the original Spanish term), an initiative for the dissemination and the study of the set of costs related to hospital activities at the patient level, which was the foundation for calculating the weights and costs of healthcare processes for patients attended in the network of hospitals belonging to the National Health System.[15] Thanks to this method, daily estimated and cumulative costs were calculated for episodes of care and for the patient journey, which in this case includes all admission, emergency and day-hospital episodes that a patient with a medical problem experiences over the observation time (1 year here) of the patients of both cohorts. Other costs, such as

total cost distribution and mean cost per episode, were calculated as well. Thus, the burden of each clinical situation in the overall cost is perfectly reflected.

Statistical analysis. Descriptive values were presented as frequencies (n, %) for categorical data, mean±standard deviation (SD) for continuous data, and median (interquartile range) for skewed continuous data. Comparisons among cohort characteristics were performed with T-Student, U Mann-Whitney, analysis of variance or Kruskal-Wallis tests, when appropriate for continuous variables and with the chi square test for categorical variables. Survival time curves were generated using the Kaplan-Meier method and statistically compared by the log rank test. Multiple logistic regression models were used to analyse the independent contribution of LVEF to mortality. Lastly, costs were presented as absolute expenditures (in euros) and percentage of total cost by follow-up time, units of patient care, clinical episode and mean per patient and day. All statistical analyses were undertaken in R studio version 4.0.3. (© 2017 The R Foundation for Statistical Computing, Vienna Austria). For all tests, p values <0.05 were considered statistically significant.

Ethics. The study complies with the Declaration of Helsinki and was approved by the Hospital Universitario 12 de Octubre Ethics Committee.

RESULTS

Patients

Between January 1st and December 31st, 2018, there were 192,733 ED visits from 123,187 adult patients. Of the total number of ED visits, 93,962 (48.8%) were for

medical reasons from 66,551 patients. A diagnosis of primary HF was registered in 1513 (2.3%) patients in the ED, with LVEF reported in 1174 (77.8%). Of them 3 patients died (0.3%) in the ED, 365 (31.1%) were discharged directly from de ED and 806 patients (68.7%) were hospitalized. In addition, there were 229 (0.3%) patients who did not have a HF diagnosis in the ED diagnostic code but were urgently admitted to the hospital and had a primary HF diagnosis at discharge (**Supplementary Figure 1**). The 113 patients of this group who had valid LVEF measurement were included as well. Hence, the global cohort of the study comprised a total of 1287 patients with a primary diagnosis of HF and known LVEF. Of them, 190 patients had HFrEF (14.7%), 146 HFmrEF (11.4%) and 951 HFpEF (73.9%). Their baseline characteristics are shown in **Table 1.** In brief, patients with HFpEF were older, more often women, and less frequently with a diagnosis of ischemic heart disease. HFpEF patients were less frequently on beta-blockers, angiotensin receptor blockers, diuretics, oral anticoagulants and platelet inhibitors. There were no differences in the proportion of patients with hypertension, diabetes, atrial fibrillation, and other comorbidities.

Baseline characteristics and initial management according to LVEF groups

Of 919 hospitalized patients, 157 were classified as HFrEF (17.1%), 108 as HFmrEF (11.8%) and 654 as HFpEF (71.2%). Differences in baseline characteristics were similar as in the whole group. HFrEF patients were treated more frequently with beta-blockers, renin-angiotensin-aldosterone system inhibitors and mineralocorticoid-receptor antagonists (**Supplementary Table 1**). HFrEF patients were initially admitted more often to the cardiology department compared with

HFmrEF and HFpEF patients (77 [49.1%] vs 39 [36.1%] vs 89 [13.6%], p<0.001) and less frequently in internal medicine (72 [45.8%] vs 69 [63.9%] vs 555 [84.9%], p<0.001). The mean and median index length of stay did not differ between HFrEF, HFmrEF and HFpEF patients (mean days, 9.8±10.5 vs. 8.3±5.6 vs. 8.2±6.3; median, 7 [5 – 10] vs 7 [5 – 10] vs 7 [4 – 10], p=0.35).

Patients discharged home directly from the ED (n=365) had similar characteristics compared with the overall population (**Supplementary Table 2**). The mean and median duration of time spent in the index ED visit were 0.7±0.7 and 3 [0 - 1] days, with no differences according to LVEF groups.

Outcomes and resource utilization by LVEF groups

Among hospitalized patients, in-hospital and 30-day mortality was similar in the three groups of LVEF, but 1-year mortality was significantly lower in HFrEF patients compared to HFmEF and HFpEF (17.2% vs. 25.9% and vs. 26.7%, p<0.001, **Figure 1**). However, LVEF was not an independent predictor of 1-year mortality after adjusting for age, sex, and cardiovascular risk factors (p=0.58).

No significant differences were observed in ED re-visits and readmissions at 30 days and 1-year. Compared with the other two groups, patients with HFpEF spent more time at home during the year of observation (**Figure 2**). Notably, the incidence of readmission was similar in all three LVEF groups at 30-day and 1-year follow-up. HFrEF patients had more outpatient consultations while ED visits after discharge were more frequent among HFmrEF and HFpEF patients.

Among patients discharged home directly from the ED, mortality rates were 3.1%, 0.0%, and 2.1% at 30 days respectively for patients with HFrEF, HFmrEF and

HFpEF (p=0.60), and 15.6%, 10.5% and 16.9% at 1 year (p=0.59). Thirty-day and 1-year new ED visits were not significantly different among groups.

Patients discharged home from the ED had a higher 30-day and 1-year re-ED visit rates across all LVEF groups (25.2% vs 16.9% at 30 days, and 76.4% vs 61.8% at 1 year, p<0.001 in both cases) **(Supplementary Table 3**). Hospitalizations after direct ED discharge were higher in the HFrEF patients (78.1%) compared with HFmrEF patients (68.4%) and HFpEF patients (48.1%, p<0.001) with HFrEF patients spending more time hospitalized (10 [4 – 19] days) during follow-up compared with those with HFmEF (6 [0 – 16] days) and HFpEF (0 [0 – 11]) (p <0.001). HFrEF patients also had more outpatient visits (11 [3 – 21]) vs. 11.5 [5 – 18] vs. 7 [3 – 12]) (p = 0.009) (**Supplementary Figure 2**).

Costs by LVEF groups

The mean cost per patient-year was €5,008 (2,747-9,590) and €1,889 (259-6,269) for the ED and hospitalized groups, respectively. In the hospitalized group, the total healthcare-related cost was highest for the HFpEF group (€4,474,176) as it was the most numerous groups, followed by the HFrEF group (€1,640,162) and the HFmrEF group (€867,351.2). However, the mean cost per patient at 1 year was highest for patients with HFrEF [€6,321(3,335-12,796)], compared with €6,170(3,189-10,484) for HFmrEF and €4,636(2,609-8,977) for HFpEF p<0.001). The mean daily cost per patient was considerably higher in HFrEF patients [€17.3 (9.1-35.1)] vs €16.9(8.7-28.7)±128.5 for HFmrEF and €12.7(7.1-24.6) for HFpEF, p<0.001) (Table 2). Patients discharged directly home from the ED incurred in significantly lower 30-day and 1-year cost with a total of €1,780,974.2 at 1-year, 81.9% (€1,460,194.6) attributed to hospitalizations (total of 374, 193 first hospitalizations after ED discharge and 181 readmissions), and 13.9% to 1,161 ED visits with no differences

between groups of LVEF (**Table 3**). Among these, patients with HFrEF had significantly higher burden of costs (mean cost per patient per year, €4,763(2,076-17,155), and a mean cost per patient per day of €13.0(5.7-47.0), compared with HFmrEF patients [€3,900(590-8,013) per year and €10.7(1.6-22.0) per day and HFpEF patients [€812(259-5,486) per year, and €2.2(0.7-15.0) per patient per day, p<0.001).

DISCUSSION

Our study shows in a contemporary cohort of patients with an acute episode of HF that those with reduced LVEF pose a greater economic burden on the healthcare system. The average cost per day over 1-year follow-up after hospitalisation was 36% higher for patients with HFrEF than for those with HFpEF, and six times higher considering the group discharged home directly from the ED. This was mainly due to higher hospitalisation and procedural costs (surgery and device implantation) in both patient groups (**Supplementary Tables 4 and 5**).

The effect of LVEF on costs in HF follow-up patients has been inconsistently assessed in few epidemiological and economic studies. The study by Liao et al. included a cohort of 495 elderly HF patients from the 1990s from a US registry and found no cost difference in 5-year follow-up of patients with LVEF ≤40% vs. >40%.[8] Another single-centre population-based study, which included patients with HF from their diagnosis throughout their lifetime, found that HFpEF (LVEF >50%) was associated with a 21% increase in inpatient cost and 24% increase in total costs compared with HFrEF.[9] Studies with more contemporary populations yield contradictory results. In a single-centre study including 564 inpatients admitted for HF, the cost per index hospitalisation was $10,286 for patients with HFrEF (≤40%)

and $8,858 for HFpEF (>40%), although this difference did not reach statistical significance (p=0.07), and was attenuated after adjusting for other variables such as age and the presence or absence of diabetes mellitus.[11] The discrepancies in the results of these studies can be explained by differences in inclusion and exclusion criteria (chronic vs. incident, stable vs. acute decompensated, primary vs. secondary HF), period of inclusion, type of healthcare system, costs included, and follow-up duration. A large (>100,000 patients) longitudinal cohort study of a prevalent HF population using linked US claims analysing in and outpatient visits during a median follow-up up 18 months with a wider perspective of cost, found a mean cost per patient of roughly $90 000, higher for HFrEF patients compared with HFpEF patients, of which, 44% was attributed to inpatient costs, 44% to outpatient costs and 12% to medication cost.[16]

Our study is one of the first to include a specific cost analysis of patients with HFmrEF. HFmrEF has traditionally been included within HFpEF, but now is considered an intermediate entity between HFrEF and HFpEF as it shows intermediate pathophysiological characteristics and prognosis. In our study, HFmrEF has an intermediate cost as well, higher than HFpEF but markedly lower than HFrEF, consistent with the hypothesis of LVEF as a continuum in chronic HF.

In our study, cost differences between LVEF groups could be explained for various reasons. First, patients with HFrEF were more frequently admitted to the cardiology department, where they had longer stays and traditionally received a greater number of specific diagnostic studies and therapies. Second, because they were more frequently followed-up in hospital outpatient offices. Finally, this result may also be motivated by the fact that patients with HFrEF had a lower mortality, which may be explained in part by the important use of disease modifying treatments.

The overall cost in our study is higher than in others of our environment, which can be mostly explained by the inclusion of patients with HF who already were hospitalized or had an ED visit, but lower to other studies with more comprehensive cost analysis.[16] Other epidemiological studies that included outpatients with HF diagnosis, with smaller proportion of hospital admissions, reported lower costs at 1-year follow-up.[12,17] Due to its inclusion criteria, our study selects a cohort of higher-risk HF patients with higher resource use and cost. Regarding the distribution of costs, with the exception of the study by Lam et al,[16] our results are in line with the available evidence attributing the majority of costs (between 50 and 90%) to hospitalisations.[5,18–20]

Although the readmission rate is similar to that reported in other studies, roughly 50% at one year,[21,22] it is noteworthy that patients with HFrEF who were discharged from the ED had the highest rate of hospitalization during follow-up, nearly 80%. This finding is consistent with others,[16] and suggests that LVEF may be a marker of risk for later admission in patients with HF, which is not included in HF emergency risk-models.[23,24] The mortality of HFrEF patients in our cohort is lower than in HFpEF patients, contrary to the results of some studies.[25,26] Multiple factors may account for this difference: HFrEF patients were younger, were managed in a highly specialised HF unit and may have had higher adherence to disease modifying drugs. Unlike other studies, we did not observe a greater comorbidity burden among patients with HFpEF.[27] The proportion of patients with HFrEF is lower than previously reported.[28] This may be partially explained by the advanced age of our population and the widespread use of echocardiography in our hospital.

Limitations. This is a single academic, urban medical centre study. Our findings may not be generalizable, particularly patterns of care that may change by

healthcare systems (i.e., rates of discharge home from ED, length of stay or readmissions). Absolute costs cannot be extrapolated to other countries as well. However, the relative differences in mortality and healthcare resource use may parallel those happening elsewhere. Although there are inherent limitations to the use of Minimum Basic Data Set data as in our retrospective study, the use of administrative information has proven to be valid to estimate outcomes in health services, compared with medical records.

CONCLUSION

Heart failure has a significant impact on healthcare resources utilization across all LVEF spectrum assessed (HFrEF, HFmEF and HFpEF). The mean cost per patient-year was €5,008 (2,747-9,590) and €1,889 (259-6,269) for the ED and hospitalized groups, respectively. Patients with HFrEF have higher follow-up costs, with a similar hospital readmission rate and lower mortality. Assessing LVEF as a predictor of admission could prevent subsequent rehospitalizations. In all LVEF groups, >80% of the expenditure is due to hospitalisation. Developing strategies to maintain outpatient stability could be a good way to contain costs.

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Declaration of interest.

Dr. Bueno receives research funding from the Instituto de Salud Carlos III, Spain (PIE16/00021 & PI17/01799, PI21/01572), Sociedad Española de Cardiología, AstraZeneca, PhaseBio and Novartis; has received consulting/speaking fees from Astra-Zeneca, Novartis, Novo Nordisk and Organon: and is a scientific advisor for MEDSCAPE-the heart.og.

FOOTNOTES

Figure 1.

Top. In-hospital, 30-day and 1-year clinical outcomes for hospitalized patients with heart failure according to left ventricular ejection fraction.

Bottom. 30-day and 1-year clinical outcomes for patients with heart failure discharged home from the emergency department according to left ventricular ejection fraction.

Figure 2. Clinical Outcomes, HEalthcare REsource utilizatioN, and relaTed costs (COHERENT) model for hospitalized patients

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TABLES AND FIGURES

Table 1. Baseline characteristics of the total cohort of patients with heart failure according to left ventricular ejection fraction

	HFrEF (n=190)	**HFmrEF** (n=146)	**HFpEF** (n=951)	**P value**
Age, years (mean±SD)	74.3 ± 13.9	78.1 ± 10.7	82.5 ± 9.2	< 0.001
Female sex, n (%)	68 (35.7%)	56 (38.3%)	610 (64.1%)	< 0.001
SBP, mmHg (mean±SD)	128.8 ± 19.5	136.6 ± 21	137.6 ± 20.1	< 0.001
DBP, mmHg (mean±SD)	75.1 ± 14.7	74.6 ± 15.3	69.4 ± 12.8	< 0.001
HR, bpm (mean±SD)	78.9 ± 18.5	80.4 ± 19.3	78.9±18.1	< 0.001
Risk factors, n (%)				
Hypertension	136 (71.5%)	117 (80.1%)	748 (78.6%)	0.103
Dyslipidaemia	68 (35.7%)	61 (41.7%)	423 (44.4%)	0.083
Diabetes	83 (43.7%)	60 (41.1%)	432 (45.4%)	0.591
Smoking	81 (42.6%)	57 (39%)	279 (29.3%)	< 0.001
Comorbidities, n (%)				
Ischemic heart disease	53 (27.9%)	45 (30.8%)	111 (11.7%)	< 0.001
Hypertensive heart disease	12 (6.3%)	11 (7.5%)	84 (8.8%)	0.484
Chronic kidney disease	17 (8.9%)	13 (8.9%)	54 (5.7%)	0.116
Atrial fibrillation	42 (22.1%)	38 (26.1%)	180 (18.9%)	0.107
Heart valve disease	17 (8.9%)	9 (6.1%)	51 (5.4%)	0.163
COPD	7 (3.7%)	5 (3.4%)	37 (3.9%)	0.958
Cancer	0 (0%)	5 (3.4%)	21 (2.2%)	-
Respiratory failure	47 (24.7%)	50 (34.2%)	319 (33.5%)	0.052
Charlson index, (mean±SD)	1.2 ± 0.46	1.2 ± 0.53	1.2 ± 0.43	< 0.001
Charlson index >2, n (%)	3 (1.5%)	4 (2.8%)	18 (1.9%)	0.796
In-hospital medical therapies				
Beta-blockers	163 (85.8%)	106 (72.6%)	445 (46.8%)	< 0.001

RAAS inhibitors				
ACE inhibitors	109 (57.4%)	74 (50.7%)	315 (33.1%)	< 0.001
ARB	64 (33.7%)	23 (15.7%)	162 (17.1%)	< 0.001
ARNI	31 (16.3%)	4 (2.7%)	0 (0%)	-
MRA	103 (54.2%)	51 (34.9%)	226 (23.7%)	< 0.001
Diuretics	173 (91.1%)	124 (84.9%)	750 (78.9%)	< 0.001
Inotropic agents	12 (6.3%)	1 (0.7%)	7 (0.7%)	< 0.001
Antithrombotic drugs				
Aspirin	60 (31.6%)	57 (39.1%)	198 (20.8%)	< 0.001
P2Y12 inhibitors	31 (16.3%)	15 (10.2%)	65 (6.8%)	< 0.001
Oral anticoagulants	103 (54.2%)	80 (54.8%)	462 (48.6%)	< 0.001
Lipid-lowering drugs	107 (56.3%)	85 (58.2%)	414 (43.5%)	< 0.001
Antidiabetic therapies				
Insulin	78 (41.1%)	54 (36.9%)	356 (37.4%)	< 0.001
Metformin	9 (4.7%)	8 (5.5%)	33 (3.5%)	< 0.001
Other antidiabetic drugs	9 (4.7%)	10 (6.8%)	38 (3.9%)	0.231

Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), standard deviation (SD), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), chronic obstructive pulmonary disease (COPD), renin-angiotensin-aldosterone system (RAAS), angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), angiotensin receptor and neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRA).

Table 2. Costs per patient journey, clinical status and episode during the first year (patients initially hospitalized)

	HFrEF (n=157)		HFmrEF (n=108)		HFpEF (n=654)		P value
	Freq	**Cost (euros)**	**Freq.**	**Cost (euros)**	**Freq.**	**Cost (euros)**	
Total patient-days, n	57,305		39,420		238,710		-
Total cost		**1,640,161.6**		**867,351.2**		**4,744,176.1**	<0.001
Median cost per patient journey		**6,321 (3,335-12,796)**		**6,170 (3,189-10,484)**		**4,636 (2,609-8,976.9)**	<0.001
Median cost per patient per day		**17.3 (9.1-35.1)**		**16.9 (8.7-28.7)**		**12.7 (7.1-24.6)**	<0.001
Use and cost per clinical status							
Mean days spent at ED	2.4 ± 2		3.1 ± 2.3		2.8 ± 2.4		0.014
Emergency Department	**123,078.7**	**7.5%**	**99,713.9**	**11.5%**	**568,344.9**	**11.9%**	
Mean days spent in-hospital	17.8±14.9		17.4±14.4		16.8±16.7		0.234
Costs for hospitalizations		**1,461,148 (89.1%)**		**735,740 (84.8%)**		**4,035,588 (85.1%)**	
Index hospitalizations		807,838 (49.2%)		374,017 (43.1%)		2,006,170 (42.2%)	
Internal Medicine		190,587 (11.6%)		202,078 (23.3%)		1,625,582 (34.3%)	
Cardiology		557,420 (33.9%)		171,939 (19.8%)		340,341 (7.2%)	
CICU		40,234 (2.5%)	-	-	-	-	
ICU		10,353 (0.63%)	-	0.0 (0.0%)		6,585 (0.14%)	
Others		9,243 (0.5%)	-	0.0 (0.0%)		33,661 (0.71%)	
Readmissions		653,309 (39.8%)		361,722 (41.7%)		2,029,417 (42.8%)	

Outpatients care station		**55,934 (3.4%)**		**31,896 (3.6%)**		**140,242 (2.9%)**	
Episodes cost per patient							
Number of episodes	838		544		3,041		
Emergency Department	352	349.6 ± 138.2	296	336.8 ± 146.5	1,657	342.9 ± 142.3	0.899
Outpatients care station	195	75 (44-472)	36	379 (145-1256)	167	273 (137-628)	< 0.001
Hospital	291	2676 (1595-4669)	212	2550 (1564-4288)	1,217	2288 (1438-3990)	0.006
Index hospitalizations	157	2606 (1472-4371)	108	2393 (1604-4549)	654	2371 (1442-4239)	0.088
Readmissions	134	2751 (1736-4901)	104	2759 (1562-4113)	563	2371 (1442-4239)	0.055

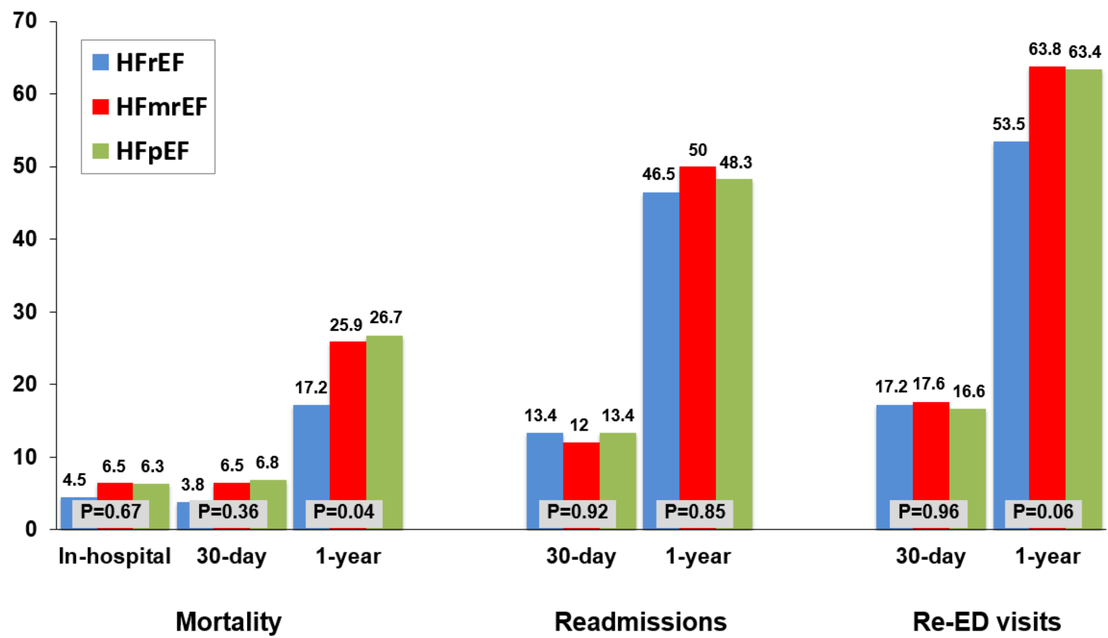
Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), frequency (freq.), emergency department (ED), intensive care unit (ICU).

Table 3. Costs per patient journey, clinical status and episode during the first year (patients initially discharged from the emergency department)

	HFrEF (n=32)		HFmrEF (n=38)		HFpEF (n=295)		P value
	Freq.	**Cost (euros)**	**Freq.**	**Cost (euros)**	**Freq.**	**Cost (euros)**	
Total patient-days, n	11,680		13,870		107,675		-
Total cost		**315,516**		**210,476**		**1,254,982**	-
Median cost per patient journey		**4,763 (2,076-17,155)**		**3,900 (590-8,013)**		**812 (259-5,486)**	<0.001
Median cost per patient per day		**13.0 (5.7-47.0)**		**10.7 (1.6-22.0)**		**2.2 (0.7-15.0)**	<0.001
Use and cost per clinical status							
Mean days spent at ED	4.1±2.3		4.6±4.1		4.1±3.1		0.724
Emergency Department		**24,549.2 (7.8%)**		**30,749.1 (14.6%)**		**191,640.7 (15.3%)**	-
Mean days spent in-hospital	15.1±17.4		10.1±11.6		8.5±15.7		<0.001
Total costs for hospitalizations		**287,07.03 (90.9%)**		**161,846.7 (76.9%)**		**1,011,322.7 (80.5%)**	-
Index hospitalizations		149,885.2 (47.5%)		78,803.2 (37.4%)		557,371.9 (44.5%)	-
Internal Medicine		30,451.6 (9.6%)		49,632.9 (23.6%)		404,538.1 (32.2%)	-
Cardiology		119,433.6 (39.7%)		20,213.4 (9.6%)		137,082.1 (10.9%)	-
ICU		-		5,888.9 (2.8%)		1,639.7 (0.1%)	-
Others		-		3,068.0 (1.4%)		14,112.1 (1.1%)	-
Readmissions		137,141.8 (43.4%)		83,043.5 (39.4%)		453,950.8 (36.1%)	-
Outpatients care station		**3,940.1 1(1.2%)**		**17,879.9 (8.5%)**		**52,018.8 (4.1%)**	-
Number of episodes	185 (100%)		209 (100%)		1,290 (100%)		
Emergency Department	102 (55.1%)	240.7±151.2	139 (66.5%	221.2±141.2	921 (71.4%)	208.1±135.3	0.15
Outpatients care station	27 (14.6%)	44 (0-231)	10 (4.8%)	1840 (455-3187)	101 (7.8%)	238 (111-526)	< 0.001
Hospital	56 (30.2%)	2415 (1547-5116)	50 (23.9%)	2649 (1654-4168)	268 (20.8%)	2541 (1556-4297)	0.883
Index hospitalizations	25 (13.3%)	2332 (1412-3879)	26 (12.4%)	2652 (1654-4375)	142 (11.0%)	2695 (1567-4496)	0.944
Readmissions	31 (16.7%)	2651 (1759-5281)	24 (11.5%)	2649 (1623-3568)	126 (9.8%)	2472 (1557-3967)	0.629

Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), frequency (freq.), emergency department (ED), cardiac intensive care unit (CICU), intensive care unit (ICU)

Figure 1



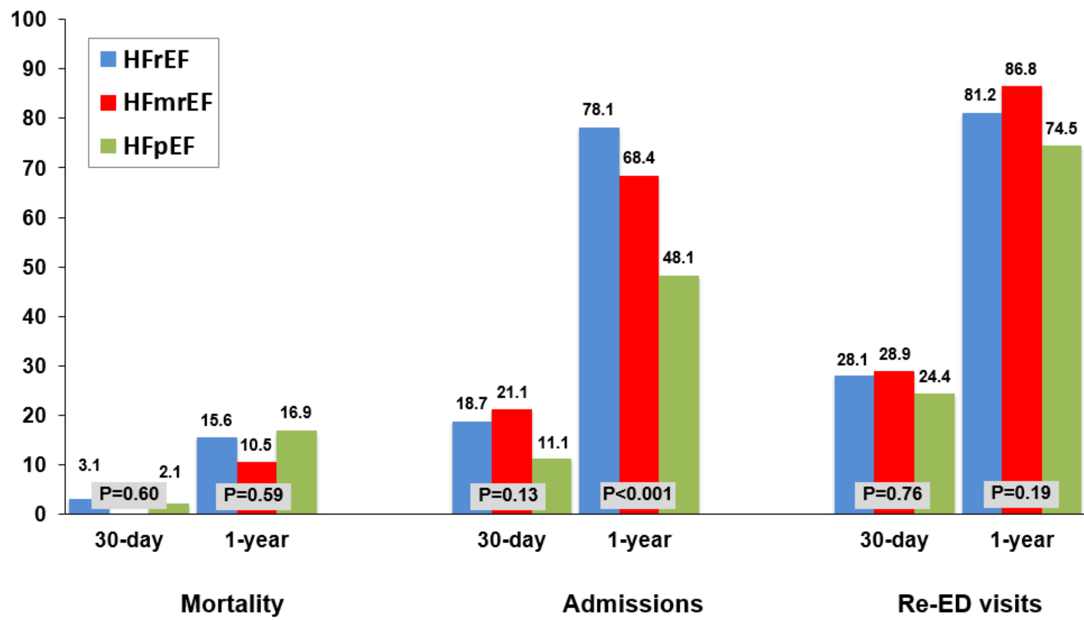
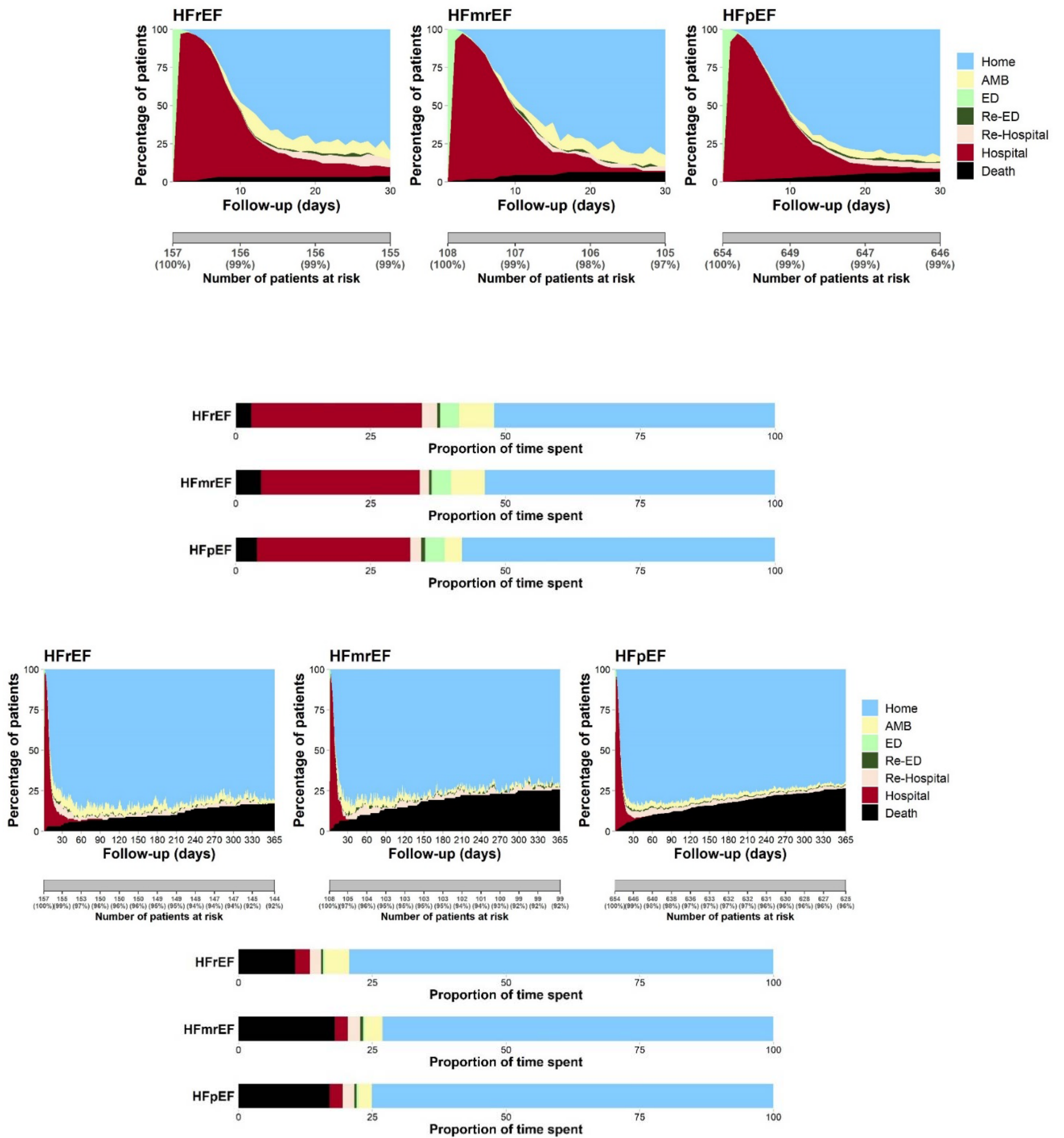


Figure 2



SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Definitions of cost components.

- ***Hospitalization***: Include the direct costs belonging to the units in which the inpatient is cared for (i.e. emergency department, wards and special units [critical care, intermediate care]), medications prescribed in the hospital and indirect allocated costs (intermediate and structural).
- ***Diagnostic tests***: Include direct costs belonging to laboratory and pathology tests, imaging studies and other diagnostic tests, as well as indirect costs (intermediate and structural) allocated to these. Blood transfusions are included here.
- **Procedures**: Include direct costs belonging to surgical and interventional procedures, such as costs of the operating room, devices, prosthesis or interventional laboratories and indirect costs (intermediate and structural) costs allocated.

SUPPLEMENTARY TABLES

Supplementary Table 1. Baseline characteristics of patients hospitalized for heart failure according to left ventricular ejection fraction

	HFrEF (n=157)	HFmrEF (n=108)	HFpEF (n=654)	P value
Age, years (mean±SD)	74.2 ± 14.2	78.9 ± 10.4	82.8 ± 9.2	< 0.001
Female sex, n (%)	59 (37.6%)	43 (39.8%)	430 (65.7%)	< 0.001
SBP, mmHg (mean±SD)	128.6 ± 20.2	135.3 ± 20.8	136.6 ± 19.8	< 0.001
DBP, mmHg (mean±SD)	75.6 ± 15.1	74.1 ± 16.1	69.2 ± 12.8	< 0.001
HR, bpm (mean±SD)	86.2 ± 20.4	80.1 ± 19.9	79.6 ± 17.7	< 0.001
Risk factors, n (%)				
Hypertension	113 (71.9%)	84 (77.7%)	520 (79.5%)	0.271
Dyslipidaemia	53 (33.7%)	39 (36.1%)	291 (44.5%)	0.022
Diabetes	66 (42.0%)	44 (40.7%)	303 (46.3%)	0.403
Smoking	64 (40.7%)	45 (41.7%)	193 (29.5%)	0.003
Comorbidities, n (%)				
Ischemic heart disease	43 (27.4%)	33 (30.6%)	84 (12.8%)	< 0.001
Hypertensive heart disease	12 (7.6%)	9 (8.3%)	74 (11.3%)	0.305
Chronic kidney disease	15 (9.6%)	11 (10.2%)	42 (6.4%)	0.202
Atrial fibrillation	38 (24.2%)	34 (31.5%)	144 (22.0%)	0.096
Heart valve disease	14 (8.9%)	9 (8.3%)	37 (5.6%)	0.239
COPD	6 (3.8%)	5 (4.6%)	32 (4.9%)	0.849
Cancer	0 (0%)	4 (3.7%)	13 (1.9%)	0.079
Respiratory failure	41 (26.1%)	47 (43.5%)	285 (43.5%)	< 0.001
Charlson index, (mean±SD)	1.2 ± 0.5	1.2 ± 0.6	1.2 ± 0.5	0.186
Charlson index >2, n (%)	3 (1.9%)	4 (3.7%)	18 (2.7%)	0.251
In-hospital medical therapies				
Beta-blockers	143 (91.1%)	87 (80.6%)	370 (56.6%)	< 0.001
RAAS inhibitors				
ACE inhibitors	98 (62.4%)	64 (59.3%)	271 (41.4%)	< 0.001
ARB	57 (36.3%)	20 (18.5%)	136 (20.8%)	< 0.001
ARNI	24 (15.3%)	2 (1.8%)	0 (0%)	< 0.001
MRA	87 (55.4%)	41 (37.9%)	183 (27.9%)	< 0.001
Diuretics	150 (95.5%)	105 (97.2%)	629 (96.2%)	0.809
Inotropic agents	11 (7.0%)	1 (0.9%)	5 (0.8%)	< 0.001
Antithrombotic drugs				
Aspirin	54 (34.4%)	45 (41.6%)	162 (24.7%)	< 0.001
$P2Y_{12}$ inhibitors	28 (17.8%)	12 (11.1%)	55 (8.4%)	0.002
Oral anticoagulants	88 (56.1%)	68 (62.9%)	383 (58.6%)	0.561
Lipid-lowering drugs	90 (57.3%)	68 (62.9%)	343 (52.4%)	0.093
Antidiabetic therapies				
Insulin	65 (41.4%)	44 (40.7%)	298 (45.6%)	0.457
Metformin	7 (4.5%)	6 (5.6%)	24 (3.7%)	0.627
Other antidiabetic drug	9 (5.7%)	9 (8.3%)	31 (4.7%)	0.241

Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), chronic

obstructive pulmonary disease (COPD), renin-angiotensin-aldosterone system (RAAS), angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), angiotensin receptor and neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRA).

Supplementary table 2. Baseline characteristics of HF patients discharged from the emergency department

	HFrEF (n=32)	HFmrEF (n=38)	HFpEF (n=295)	P value
Age, years (mean±SD)	74.1 ± 12.6	75.5 ± 11.4	81.9 ± 9.4	< 0.001
Female sex, n (%)	9 (28.1%)	13 (34.2%)	178 (60.3%)	< 0.001
SBP, mmHg (mean±SD)	130.1 ± 15.3	140.1 ± 21.7	139.9 ± 20.4	0.039
DBP, mmHg (mean±SD)	72.3 ± 12.8	76.3 ± 12.7	70.1 ± 12.9	0.027
HR, bpm (mean±SD)	79.6 ± 19	81.4 ± 17.5	77.1 ± 19.1	0.187
Risk factors, n (%)				
Hypertension	23 (71.8%)	33 (86.8%)	227 (76.9%)	0.192
Dyslipidaemia	15 (46.8%)	22 (57.9%)	131 (44.5%)	0.29
Diabetes	16 (50%)	16 (42.1%)	128 (43.4%)	0.754
Smoking	16 (50%)	12 (31.6%)	85 (28.8%)	0.048
Comorbidities, n (%)				
Ischemic heart disease	10 (31.2%)	12 (31.6%)	27 (9.1%)	< 0.001
Hypertensive heart disease	0 (0%)	2 (5.3%)	10 (3.4%)	0.192
Chronic kidney disease	2 (6.2%)	2 (5.3%)	12 (4.1%)	0.816
Atrial fibrillation	4 (12.5%)	4 (10.5%)	36 (12.2%)	0.953
Heart valve disease	3 (9.4%)	0 (0%)	14 (4.8%)	0.176
COPD	1 (3.1%)	0 (0%)	5 (1.7%)	0.584
Cancer	0 (0%)	1 (2.6%)	8 (2.8%)	0.641
Respiratory failure	5 (15.6%)	3 (7.9%)	33 (11.2%)	0.593
Charlson index, (mean±SD)	1.12 ± 0.34	1.13 ± 0.34	1.09 ± 0.3	0.231
Charlson index >2, n (%)	0 (0%)	0 (0%)	0 (0%)	-
In-hospital medical therapies				
Beta-blockers	20 (62.5%)	19 (50%)	75 (25.4%)	0.007
RAAS inhibitors				
ACE inhibitors	11 (34.4%)	10 (26.3%)	44 (14.9%)	0.4
ARB	7 (21.9%)	3 (7.9%)	26 (8.8%)	0.42
ARNI	7 (21.9%)	2 (5.3%)	0 (0%)	< 0.001
MRA	16 (50%)	10 (26.3%)	43 (14.6%)	0.008
Diuretics	23 (71.9%)	19 (50%)	121 (41.1%)	0.49
Inotropic agents	1 (3.1%)	0 (0%)	2 (0.7%)	0.533
Antithrombotic drugs				
Aspirin	6 (18.8%)	12 (31.6%)	36 (12.2%)	0.039
P2Y12 inhibitors	3 (9.4%)	3 (7.9%)	10 (3.4%)	0.567
Oral anticoagulants	15 (46.9%)	12 (31.6%)	79 (26.8%)	0.815
Lipid-lowering drugs	17 (53.1%)	17 (44.7%)	71 (24.1%)	0.091
Antidiabetic therapies				
Insulin	13 (40.6%)	10 (26.3%)	58 (19.7%)	0.719
Metformin	2 (6.2%)	2 (5.3%)	9 (3.1%)	0.929
Other antidiabetic drugs	0 (0%)	0 (0%)	7 (2.3%)	-

Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), chronic

obstructive pulmonary disease (COPD), renin-angiotensin-aldosterone system (RAAS), angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), angiotensin receptor and neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRA).

Supplementary Table 3. Clinical outcomes of heart failure patients initially hospitalized or discharged from the emergency department according to left ventricular ejection fraction

	HFrEF (N= 190)		P value	HFmrEF (N= 146)		P value	HFpEF (N= 951)		P value
	Admitted (n=157)	**Discharged (n=33)**		**Admitted (n=108)**	**Discharged (n=38)**		**Admitted (n=654)**	**Discharged (n=297)**	
30-day mortality	6 (3.8)	2 (6.0)	0.916	7 (6.5)	0 (0)	0.243	45 (6.8)	8 (2.7)	0.014
365-day mortality	27 (17.2)	6 (18)	0.999	28 (25.9)	4 (10.5)	0.081	175 (26.7)	52 (17.5)	0.002
In-hospital mortality	7 (4.5)	-	-	7 (6.5)	-	-	41 (6.3)	-	-
30-day admissions	157 (100)	6 (18)	<0.001	108 (100)	8 (21.1)	<0.001	654 (100)	33 (10.0)	<0.001
365-day admissions	157 (100)	25 (75.0)	<0.001	108 (100)	26 (68.4)	<0.001	654 (100)	142 (47.8)	<0.001
30-day re-admissions	21 (13.4)	1 (3.0)	0.091	13 (12.0)	1 (2.6)	0.090	88 (13.4)	3 (1.0)	<0.001
365-day re-admissions	73 (46.5)	14 (42)	0.669	54 (50.0)	15 (39.4)	0.336	314 (48.3)	68 (22.9)	<0.001
30-day re-ED visits	27 (17.0)	9 (27.0)	0.272	19 (17.6)	11 (28.9)	0.208	109 (16.6)	72 (24.0)	0.007
365-day re-ED visits	84 (53.5)	26 (78.0)	0.013	69 (63.8)	33 (86.8)	0.014	415 (63.4)	220 (74.0)	<0.001

Abbreviations: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF), emergency department (ED).

Supplementary Table 4. Cost components in euros per patient and episode in patients with heart failure initially hospitalized, according to left ventricular ejection fraction

	HFrEF (n=157)	HFmrEF (n=108)	HFpEF (n=654)	P value
Hospitalization				
Median cost per patient	3390 (2054 – 7334)	3913 (2028 – 7426)	3202 (1722 - 6212)	0.088
Median cost per episode	2048 (1308 - 3340)	2138 (1326 – 3320)	1977 (1182 - 3346)	0.248
Diagnostic tests				
Median cost per patient	195 (102 - 556)	234 (95 – 451)	157 (67 - 404)	0.011
Median cost per episode	99 (47-249)	101 (45- 230)	83 (34-209)	0.203
Procedures				
Median cost per patient	71 (25-1369)	26 (24-661.7)	25 (0-376.7)	<0.001
Median cost per episode	25 (0-415.5)	25 (0-43.7)	2 (0-60)	0.407

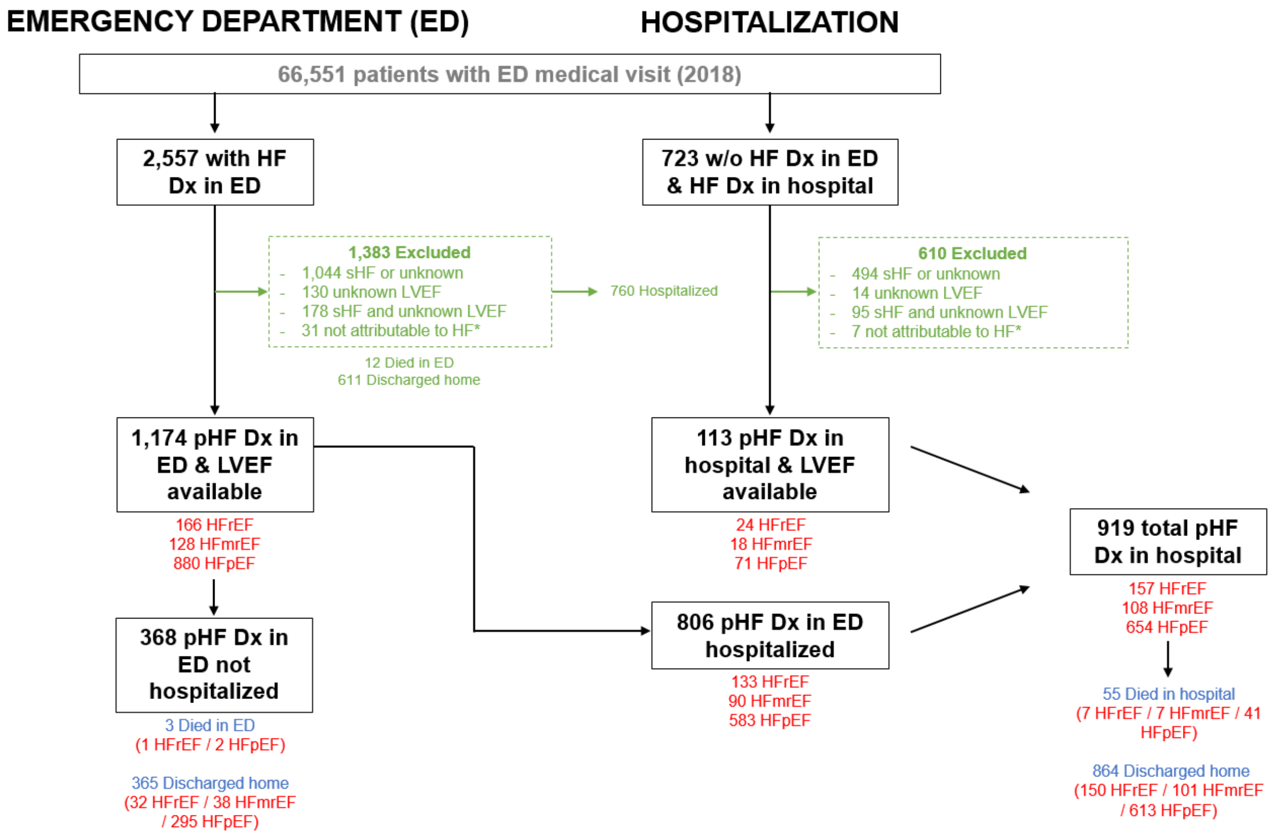
*Variances are not significantly homogeneous. **Abbreviations**: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF).

Supplementary Table 5. Cost components in euros per patient and episode in patients with heart failure initially discharged from the emergency department, according to left ventricular ejection fraction

	HFrEF (n=33)	HFmrEF (n=38)	HFpEF (n=297)	P value
Hospitalization				
Median cost per patient	3387.9 (1798 – 9027)	3273.5 (1608 – 5079.9)	3587.8 (1961.9 – 6894.7)	0.248
Median cost per episode	1964 (1175-3039.9)	1744.5 (808-2988)	2150.5 (1218.8 – 3545.3)	0.248
Diagnostic tests				
Median cost per patient	289 (93 - 534)	173 (54 - 271)	172.5 (53 - 385)	0.203
Median cost per episode	79 (22.5 - 197)	63.5 (24 - 114)	81.5 (33 – 228.5)	0.203
Procedures				
Median cost per patient	33 (19-1648)	25 (0-779.5)	25 (0-483.5)	0.358
Median cost per episode	21.5 (0-121.5)	0 (0-132.2)	0 (0-208.5)	0.407

*Variances are not significantly homogeneous. **Abbreviations**: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF).

Supplementary Figure 1. Flow chart of the populations included in the study



Abbreviations: heart failure (HF), diagnosed (Dx), primary heart failure (pHF), secondary heart failure (sHF), left ventricular ejection fraction (LVEF), heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with preserved ejection fraction (HFpEF). *Variances are not significantly homogeneous

Supplementary Figure 2. Clinical Outcomes, HEalthcare REsource utilizatioN, and relaTed costs (COHERENT) model for heart failure patients discharged home from the emergency department