# Impact of left ventricular ejection fraction phenotypes on healthcare-resource utilization in hospitalized heart failure: A secondary analysis of REPORT-HF

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**Running head:** Healthcare resource utilization in hospitalized heart failure

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**Background:** Evidence on healthcare resource utilization (HCRU) for hospitalized patients with heart failure (HF) and reduced (HFrEF), mildly-reduced (HFmrEF) and preserved (HFpEF) left ventricular ejection fraction (LVEF) is limited.

**Methods:** We analysed HCRU in relation to LVEF phenotypes, clinical features and in-hospital and 12-month outcomes in 16,943 patients hospitalized for HF in a worldwide registry.

**Results:** HFrEF was more prevalent (53%) than HFmrEF (17%) or HFpEF (30%). Patients with HFmrEF and HFpEF were older, more often women, with milder symptoms and more comorbidities, but differences were not pronounced. HCRU was high in all three groups; 2 or more in- and out-hospital services were required by 51%, 49% and 52% of patients with HFrEF, HFmrEF and HFpEF, respectively, and ICU by 41%, 41% and 37%, respectively.Hospitalization length was similar (median, 8 days). Discharge prescription of neurohormonal inhibitors was <80% for each agent in HFrEF and only slightly lower in HFmrEF and HFpEF (74% and 67%, respectively for beta-blockers). Compared to HFrEF, 12-month all-cause and cardiovascular mortality were lower for HFmrEF [adjusted hazard ratios, 0.76 (0.68-0.84) and 0.77 (0.68-0.88)] and HFpEF [0.62 (0.56-0.68) and 0.60 (0.53-0.68)]; 12-month HF hospitalization was also lower for HFpEF and HFmrEF (21% and 20% versus 25% for HFrEF). In-hospital mortality, 12-month non-cardiovascular mortality and 12-month all-cause hospitalization were similar among groups.

**Conclusions:** In patients hospitalized for HF, overall HCRU was similarly high across LVEF spectrum, reflecting the subtle clinical differences among LVEF phenotypes during hospitalization. Discharge prescription of neurohormonal inhibitors were suboptimal in HFrEF and lower but significant in patients with HFpEF and HFmrEF, who had better

long-term cardiovascular outcomes than HFrEF, but similar risk for non-cardiovascular events.

**Keywords:** heart failure, prognosis, mortality, heart failure hospitalization, left ventricular ejection fraction, pharmacotherapy.

## Introduction

Heart failure (HF) is characterized by considerable heterogeneity in terms of aetiology, clinical presentation, comorbid conditions, severity, response to therapies and outcomes (1). In an effort to categorize this heterogeneous syndrome and gain more clinically meaningful insights, international societies have proposed the classification of HF into three phenotypes based on left ventricular ejection fraction (LVEF): HF with reduced (HFrEF), mildly reduced (HFmrEF) and preserved LVEF (HFpEF) (2,3). This classification echoes pre-existing evidence on the prognostic value of LVEF (4), as well as the design and outcomes of clinical trials on neurohormonal inhibitors.

Heart failure imposes a significant healthcare resource utilization (HCRU), resulting mainly from hospitalization (5). Although previous studies have addressed the differences among the three LVEF-based HF phenotypes (6,7,8,9,10,11), evidence on hospitalized patients with HF in terms of in-hospital and post-discharge HCRU in relation to clinical characteristics and outcomes is limited. We sought to address the above issue using a large contemporary global HF cohort that provides real-world evidence on the current clinical characteristics, treatment patterns, healthcare resource utilization and outcomes of hospitalized patients with HF across the world.

## Patients and Methods

We performed a secondary analysis of REPORT-HF, a large, contemporary registry of 18,553 patients hospitalized for HF in 358 hospitals in 44 countries across Europe, North, Central and South America, Africa, Middle East, Asia and the Pacific; the study protocol has been described in detail elsewhere (12,13). In brief, REPORT-HF recruited

adult patients hospitalised due to a primary diagnosis of HF, as defined by treating physicians. All patients or legal representatives were asked to provide written informed written consent. The only exclusion criteria were failure or unwillingness to give consent or participation in a clinical trial with investigational treatments. Data collected during index hospitalization included demographics, medical history, vital signs, physical examination findings, laboratory test values, therapies and procedures during hospitalization, admission and discharge medications and admission and hospitalization details. Follow-up information was collected via standardized telephone interviews performed at 6 and 12 months after index hospitalization, unless a regular follow-up visit was planned at investigator site. Vital status was supplemented by national databases where available. Causes of death were classified as cardiovascular, non-cardiovascular, or unknown and ascertained by local investigators. At 6-months, data on medications was collected through follow-up call or visit, primary care provider or both

All patients with documented baseline LVEF were considered for analysis. We compared patient characteristics among the three LVEF phenotypes defined as HFrEF (LVEF <40%), HFmrEF (LVEF 40-49%) and HFpEF (LVEF ≥50%) (3). Comparisons included baseline demographics and clinical features, in-hospital treatment, HCRU, discharge medications, in-hospital mortality (index hospitalization), all-cause and cardiovascular (CV) mortality at 12 months post-discharge and all-cause and HF hospitalization at 12 months. We further sought to identify predictors of all-cause and CV death among baseline characteristics and HCRU.

***Statistical analysis***

Categorical variables are expressed as number of patients and proportions and

numerical variables as means and standard deviations or median and interquartile range according to whether they were normally distributed or not. Baseline features, in-hospital therapies and discharge medications were compared using a chi square test, one-way analysis of variance (ANOVA) or the Wilcoxon Rank-Sum test where appropriate. Long-term outcomes were analyzed with Kaplan-Meier survival curves and multivariate Cox regression analyses. Confounders were selected on clinical relevance and prior publications (12,13). Hazard ratios were mutually adjusted for age, sex, history of hypertension, atrial fibrillation, chronic obstructive pulmonary disease (COPD), chronic kidney disease, coronary artery disease and usage of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRA) and diuretics. In addition, we added patient's ethnicity, HF diagnosis (decompensated chronic HF vs new-onset HF), number of in-hospital services used and mode of transport to reach the hospital. The proportionality of hazards assumption was checked visually using Schoenfeld residuals, which did not show a violation. Multicollinearity was assessed using the variance inflation factor (VIF). The VIF was below 10 for all variables except for age. However, due to the importance of age for outcome, we kept this variable in the model. We used case-wise deletion of patients with missing data for any of the possible confounders in the total Cox regression model due to low missingness of data. The complete model included 16,071 patients out of 16,943 patients discharged alive, equating the exclusion of only 5.1% of patients in the multivariable model. When analyzing CV mortality, non-CV and unclassified mortality were considered as competing risks; accordingly, when analyzing non-CV mortality, CV and unclassified mortality were considered as competing risks. Sensitivity analyses were performed in patients with LVEF measured

during the index hospitalization. A p value of <0.05 was considered statistically significant. Differences between groups should be interpreted based on their clinical significance and magnitude, not on the p-value alone. Statistical analyses were performed using STATA, version 17.

## Results

### *Baseline characteristics*

Out of a total of 18,553 patients, 16,943 (91%) had a documented LVEF and were included in this study; among these patients, LVEF was measured during the index hospitalization in 13,933 (82%). Among the 16,943 patients, 30% had HFpEF, 17% HFmrEF and 53% HFrEF.

The baseline patient characteristics are presented in Table 1. Patients with HFpEF and HFmrEF were older compared to those with HFrEF, and the proportion of women increased with an increasing LVEF. Distribution of race, and geographical region also differed among the three LVEF groups. Patients with HFpEF and HFmrEF were more likely to have new-onset HF compared to those with HFrEF (47% and 46% versus 39%) and more often had mild symptoms, classified as New York Heart Association (NYHA) class I or II (26% and 24% versus 20%). Patients with HFpEF and HFmrEF presented with higher systolic blood pressure compared to HFrEF. Comorbid conditions were more prevalent in HFpEF and HFmrEF compared to HFrEF, with more striking differences being noticed in CV comorbidities, including hypertension (74%, 71% and 56%, respectively), atrial fibrillation or flutter (40%, 33% and 26%, respectively) and valvular heart disease (28%, 22% and 15%, respectively). Diabetes mellitus was prevalent in all HF phenotypes, but

numerically highest in the HFmrEF population (41% versus 39% in HFpEF and 37% in HFrEF). Anemia was prevalent in 45% in HFrEF, 50% in HFmrEF and 51% in HFpEF, chronic kidney disease in 19%, 22% and 23%, respectively, and COPD/asthma in 13%, 14% and 17%, respectively .

***In-hospital management***

In-hospital management and HCRU are outlined in Table 2. During index hospitalization, ICU admittance was greater in HFrEF and HFmrEF (41% for both) compared to HFpEF (37%). The use of diuretics did not differ between groups, but patients with HFpEF and HFmrEF were more frequently treated with vasodilators and less frequently with inotropes than HFrEF. The time to intravenous therapies also differed between groups (median, 46 min in HFpEF and HFmrEF versus 1 hour in HFrEF). Patients with HFmrEF more frequently underwent a percutaneous coronary intervention (PCI) compared to HFrEF and HFpEF (9% versus 6% and 4%, respectively), while the use of coronary artery bypass grafting did not differ among the groups (mean, 1%). The median total hospitalization length was 8 days in all three groups.

Upon discharge, drug prescription rates, including neurohormonal inhibitors and diuretics, differed among the groups,. The prescription rates were less than 80% for each of the three guideline-recommended medical therapies in HFrEF (70% for ACEi/ARB, 77% for beta-blockers, 60% for MRA). The corresponding rates for these drugs in HFmrEF were 66%, 74% and 43% and in HFpEF, 61%, 67% and 37%, respectively. Prescription rates of diuretics were 87% in HFrEF, 82% in HFmrEF and 80% in HFpEF.

***Healthcare resource utilization and outcomes***

Table 3 summarizes HCRU in the three LVEF groups. Overall, HCRU, in terms of in-hospital and out-hospital services used, in-hospital interventions and total in-hospital therapies differed among groups (all p <0.001). For example, 2 in- and out-hospital services were required by 51%, 49% and 52% of patients with HFrEF, HFmrEF and HFpEF, respectively, while 3 services were used by 15%, 13% and 10% of patients, respectively.The number of medications prescribed at discharge also differed among the three groups (overall p <0.001). For example, 4 medications were prescribed in 35% of patients with HFrEF versus 22% of those with HFmrEF and 15% of those with HFpEF. Total re-hospitalizations at 12 months did not differ among the groups (38% in HFrEF and HFmrEF, 39% in HFpEF).

***In-hospital and long-term outcomes***

In-hospital and/or 12-month outcomes are reported in Tables 4 and 5 and Figure 1. In-hospital mortality was similar among the three LVEF groups, being 2% in HFmrEF and HFpEF and 3% in HFrEF. In contrast, all-cause mortality rates at 12 months post-discharge differed among the groups, being lower in HFpEF (16%), intermediate in HFmrEF (18%) and higher in HFrEF (22%). This difference persisted after adjustment for demographics, comorbidities and discharge medications (Table 5). Patients with HFpEF had a 38% lower adjusted risk of all-cause death and a 40% lower adjusted risk of CV death compared to those with HFrEF. Similarly, patients with HFmrEF had a 24% lower adjusted risk of all-cause death and a 23% lower adjusted risk of CV death compared than those with HFrEF. Non-CV mortality and all-cause hospitalization was similar in the three groups, while HF hospitalization was lower in HFpEF and HFmrEF compared to HFrEF (21% and 20% versus 25%, respectively). In sensitivity analyses restricted to patients with LVEF measured during the index hospitalization, results remained similar.

**Discussion**

This contemporary and truly global cohort of nearly 17,000 hospitalized patients with HF provides real-world evidence on the clinical features, treatment patterns, HCRU and long-term prognosis of these patients, categorized according to LVEF, a widely used, yet questioned, parameter for HF phenotyping. In this cohort, 30% of patients were categorized as HFpEF, 17% as HFmrEF and 53% as HFrEF. In contrast to previous cohorts (6), hospitalized patients with normal LVEF values are highly prevalent and are now increasingly being recognized as a true HF phenotype. According to our findings, hospitalized HFpEF patients required considerable HCRU, comparable to that of patients with impaired LVEF. In addition, despite the lack of GDMT at the time when this study was performed, patients with HFpEF were still treated with many cardioactive medications because of their comorbidities and risk factors.

Clinical characteristics at presentation differed significantly among the three LVEF phenotypes, but differences were not generally pronounced or clinically significant. A substantial proportion of patients in all three phenotypes had CV and non-CV comorbidities that were statistically more frequent in HFpEF and HFmrEF than in HFrEF. However, striking differences were noticed only in CV comorbidities, including arterial hypertension, atrial fibrillation and valvular disease. Differences in the prevalence of non-CV coexistent conditions, including diabetes, anemia, chronic obstructive lung disease and chronic kidney disease were not marked.

Overall, there were no clinically meaningful differences in HCRU among the three groups. As a result, HCRU remains high among patients with HF, regardless of LVEF phenotype,

despite the general perception that patients with higher LVEF values may be less sick. This is probably related to the higher age and prevalence of comorbidities of these latter patients. A considerable delay in the institution of intravenous therapies was noticed in HFrEF patients compared to the other two groups, including inotropes that were started after a median of 5 hours following admission. Although we have no evidence to compare intravenous treatment onset with the evolution of individual patient condition, the timely onset of therapy in hospitalized patients with HF seems to remain an unmet need (16).

The prescription rates of neurohormonal inhibitors were generally higher in HFrEF, intermediate in HFmrEF and lower in HFpEF. However, these rates were low in the case of HFrEF patients, being lower than 80% for each one the three main drug classes, and lower than those reported by previous registries from Europe (7). This finding may reflect significant regional differences, as reported by the current and previous studies (13,17,18). The observed inequalities may partly result from different local protocols and recommendations, but also variable levels of guideline implementation and physicians training. Interestingly, the prescription rates of neurohormonal inhibitors in patients with HFpEF and HFmrEF, although lower than in HFrEF, were generally high, despite the fact that these drugs are not recommended as HF medications in these patients. In the PARAGON trial on sacubitril/valsartan in patients with LVEF >40%, the corresponding prescription rates were even higher (19). This probably reflects the high prevalence of CV comorbidities observed in these patients, with arterial hypertension being present in almost 75% of those with HFpEF. Higher prescription of guideline-directed medical therapies (GDMT) at discharge has been associated with better short and long-term

outcomes in HF patients, while the initiation and rapid titration of GDMT before and shortly after discharge is feasible, and safe (20,21,22).

There were no differences among the three LVEF groups in in-hospital mortality and non-CV mortality or all-cause hospitalization at 12 months post-discharge. In contrast, all-cause mortality at 12 months was higher in HFrEF, intermediate in HFmrEF and lower in HFpEF, which actually resulted from similar differences in CV mortality. These findings are consistent with the results of the ESC Heart Failure Long-Term Registry, in which the 12-month all-cause mortality in ambulatory patients with HF was higher in HFrEF, intermediate in HFmrEF and lower in HFpEF (8.8%, 7.6% and 6.3%, respectively) (7). One may speculate that the intermediate risk of CV mortality in HFmrEF patients reflects the also intermediate prescription rates of neurohormonal inhibitors. In fact, secondary analyses and meta-analyses of clinical trials have shown that the response to neurohormonal inhibitors, including candesartan, spironolactone, beta-blockers and sacubitril/valsartan, in patients with a LVEF in the range between 40% and 50-57% is rather consistent with that of patients with LVEF <40% (19,23,24,25). It should be stressed though that in the present analysis, adjustment for discharge medications did not modify the survival patterns. On the other hand, the response of HFmrEF patients to neurohormonal inhibitors in the aforementioned studies is in contrast to their similar clinical features with HFpEF patients in this study. The clinical relevance of defining an intermediate LVEF category and the extent to which this represents a transition phase between normal and the reduced LVEF has been previously discussed (26).

Phenotyping HF using LVEF may not capture the heterogeneity of HF and thus categorize patients sufficiently. A combination of markers reflecting multiple metabolic, immune, signal transduction and cell interaction processes and pathways is probably more

suitable to capture the heterogeneity of HF syndromes and thus to categorize patients more effectively (27). Two additional issues are relevant in this regard, the imprecision of LVEF measurements and the longitudinal changes in LVEF (28,29)(30). On the other hand, evidence from the sodium glucose co-transporter 2 inhibitor trials in HF, have shown that dapagliflozin and empagliflozin are effective in reducing the risk of CV death or HF events across the spectrum of LVEF [31,32]. Similarly, in the STRONG-HF trial, the rapid up-titration of GDMT at discharge and shortly after was safe and effective across the LVEF spectrum [22]. This recent evidence further questione the clinical relevance of the LVEF-based classification.

The general limitations of REPORT-HF have been previously acknowledged (13). One major limitation of the study is that recently introduced GDMT such as sacubitril valsartan or sodium glucose cotransporter 2 inhibitors could not be included as the cohort ranged from 2014 to 2017. In addition, in the present analysis, it is not known to what extent the observed differences regarding in-hospital management and discharge prescription patterns among the three LVEF groups reflect differences in clinical status and in-hospital course, local protocols or physicians' inertia.

In conclusion, in a contemporary, large, global cohort of hospitalized patients with HF, clinical differences among the proposed LVEF-based HF phenotypes were present but generally not marked. Despite differences in post-discharge all-cause and CV mortality, HCRU was high in all LVEF categories while in-hospital and long-term non-CV mortality rates did not differ among the phenotypes. Both the use of neurohormonal inhibitors and the risk of all-cause and CV death were lower in HFpEF, intermediate in HFmrEF and higher in HFrEF. Still, prescription rates of neurohormonal inhibitors were low in HFrEF, while a significant proportion of HFpEF and HFmrEF patients were prescribed these drugs

due to the high burden of CV comorbidities. Health economic analyses of real-world evidence such as that presented herein would provide useful insights into the current financial burden of the HF syndrome.

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**Figure legends**

**Central illustration:** Healthcare resource utilization and outcomes in hospitalized heart failure patients across left ventricular ejection fraction phenotypes: A REPORT-HF sub-analysis (HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, HF with reduced LVEF; HFmrEF, HF with mid-range or mildy reduced LVEF; HFpEF, HF with preserved LVEF; CV, cardiovascular).

**Figure 1:** Kaplan-Meier curves for all-cause (upper panel), cardiovascular (middle panel) and non-cardiovascular (lower panel) mortality at 12 months post-discharge in hospitalized heart failure patients by left ventricular ejection fraction phenotype (HFrEF, heart failure with reduced LVEF; HFmrEF, heart failure with mid-range or mildy reduced LVEF; HFpEF, heart failure with preserved LVEF).

**Figure 2:** Number of in- and out-hospital services used and in-hospital mortality by left ventricular ejection fraction phenotype (HFrEF, heart failure with reduced LVEF; HFmrEF, heart failure with mid-range or mildy reduced LVEF; HFpEF, heart failure with preserved LVEF).

## Tables

**Table 1:** Baseline clinical characteristics of hospitalized heart failure patients by left ventricular ejection fraction phenotype

| | HFrEF | HFmrEF | HFpEF | *P-value* |
|---|---|---|---|---|
| **N** | 8904 | 2871 | 5168 | |
| **Demographics** | | | | |
| Age (years) | 64 (55, 74) | 69 (59, 78) | 71 (61, 79) | <0.001 |
| Gender, n(%) | | | | <0.001 |
| Male | 6418 (72%) | 1745 (61%) | 2275 (44%) | |
| Female | 2486 (28%) | 1126 (39%) | 2893 (56%) | |
| Race, n(%) | | | | <0.001 |
| Caucasian | 4322 (49%) | 1572 (55%) | 2986 (58%) | |
| Black | 521 (6%) | 74 (3%) | 243 (5%) | |
| Asian | 2832 (32%) | 954 (33%) | 1432 (28%) | |
| Native American | 179 (2%) | 54 (2%) | 80 (2%) | |
| Pacific Islander | 4 (<1%) | 1 (<1%) | 2 (<1%) | |
| Other | 1046 (12%) | 216 (8%) | 425 (8%) | |
| Region, n(%) | | | | <0.001 |
| Central & South America | 1303 (15%) | 333 (12%) | 686 (13%) | |
| Eastern Europe | 955 (11%) | 525 (18%) | 1125 (22%) | |
| Eastern Mediterranean & Africa | 1199 (13%) | 356 (12%) | 489 (9%) | |
| North America | 888 (10%) | 164 (6%) | 523 (10%) | |
| Southeast Asia | 1249 (14%) | 383 (13%) | 470 (9%) | |
| Western Europe | 1770 (20%) | 543 (19%) | 916 (18%) | |
| Western Pacific | 1540 (17%) | 567 (20%) | 959 (19%) | |
| **Clinical features** | | | | |
| New-onset heart failure | 3448 (39%) | 1317 (46%) | 2411 (47%) | <0.001 |
| Heart failure aetiology | | | | <0.001 |
| Ischemic, n(%) | 3367 (38%) | 1128 (39%) | 1241 (24%) | |
| Non-ischemic, n(%) | 4111 (46%) | 1308 (46%) | 3119 (60%) | |
| Unknown | 1426 (16%) | 435 (15%) | 808 (16%) | |
| NYHA class, n(%) | | | | <0.001 |
| I | 345 (4%) | 156 (5%) | 303 (6%) | |
| II | 1449 (16%) | 546 (19%) | 1042 (20%) | |
| III | 2504 (28%) | 795 (28%) | 1359 (26%) | |
| IV | 1209 (14%) | 299 (10%) | 455 (9%) | |
| Heart rate (bpm) | 89 (75, 104) | 85 (73, 100) | 82 (70, 100) | <0.001 |
| Systolic blood pressure (mmHg) | 124 (110, 140) | 136 (120, 155) | 139 (120, 160) | <0.001 |
| Diastolic blood pressure (mmHg) | 79 (68, 90) | 80 (70, 90) | 80 (70, 90) | <0.001 |
| Signs and symptoms, n(%) | | | | |
| Dyspnea at rest | 6456 (83%) | 2183 (84%) | 3782 (82%) | 0.16 |
| Orthopnea | 5572 (78%) | 1820 (76%) | 3226 (77%) | 0.081 |
| Peripheral edema | 5250 (67%) | 1767 (68%) | 3392 (72%) | <0.001 |
| Pulmonary rales | 4628 (65%) | 1721 (70%) | 3078 (70%) | <0.001 |
| **Comorbidities, n(%)** | | | | |
| Hypertension | 4956 (56%) | 2026 (71%) | 3831 (74%) | <0.001 |
| Atrial fibrillation/flutter | 2274 (26%) | 957 (33%) | 2070 (40%) | <0.001 |
| Valvular Heart Disease | 1363 (15%) | 635 (22%) | 1469 (28%) | <0.001 |
| COPD/Asthma | 1142 (13%) | 412 (14%) | 893 (17%) | <0.001 |
| Anemia | 3986 (45%) | 1437 (50%) | 2610 (51%) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Diabetes mellitus | 3306 (37%) | 1184 (41%) | 2001 (39%) | <0.001 |
| Chronic Kidney Disease | 1713 (19%) | 626 (22%) | 1168 (23%) | <0.001 |

HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure heart failure with mid-range or mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease.

**Table 2:** Healthcare resource utilization, in-hospital management and discharge medications of hospitalized heart failure patients by left ventricular ejection fraction phenotype

| | HFrEF | HFmrEF | HFpEF | *P-value* |
|---|---|---|---|---|
| **N** | 8904 | 2871 | 5168 | |
| **Transportation to hospital, n(%)** | | | | <0.001 |
| Patient's own transportation | 6151 (69%) | 1822 (64%) | 3390 (66%) | |
| Ambulance | 2080 (23%) | 830 (29%) | 1424 (28%) | |
| Other | 664 (7%) | 217 (8%) | 350 (7%) | |
| **Hospital point of entry, n(%)** | | | | <0.001 |
| Emergency Room | 5634 (63%) | 1729 (60%) | 3119 (60%) | |
| Heart Failure Facilities | 542 (6%) | 130 (5%) | 225 (4%) | |
| Cardiac Ward | 1542 (17%) | 535 (19%) | 1098 (21%) | |
| Cardiac/Coronary Care Unit | 682 (8%) | 278 (10%) | 400 (8%) | |
| General/Medical/Surgical ICU | 199 (2%) | 98 (3%) | 121 (2%) | |
| Other | 298 (3%) | 100 (3%) | 201 (4%) | |
| **Patient in-hospital pathway, n(%)** | | | | |
| ED | 5862 (66%) | 1806 (63%) | 3241 (63%) | <0.001 |
| ICU/CCU | 3649 (41%) | 1183 (41%) | 1911 (37%) | <0.001 |
| General ward | 6101 (69%) | 1868 (65%) | 3427 (66%) | 0.001 |
| **Intravenous medication, n(%)*** | | | | |
| Vasodilators | 1263 (16%) | 567 (22%) | 878 (19%) | <0.001 |
| Inotropes | 967 (12%) | 203 (8%) | 313 (7%) | <0.001 |
| Diuretics | 6775 (87%) | 2216 (87%) | 3973 (87%) | 0.850 |
| **Time to treatment, min** | | | | |
| Time to any | 61 (14, 187) | 46 (8, 155) | 46 (5, 160) | <0.001 |
| Time to vasodilators | 75 (20, 278) | 56 (10, 174) | 52 (12, 185) | <0.001 |
| Time to inotropes | 294 (58, 2530) | 175 (24, 1710) | 176 (22, 2127) | <0.001 |
| Time to diuretics | 85 (24, 240) | 60 (13, 196) | 64 (12, 206) | <0.001 |
| **In-hospital procedures, n(%)** | | | | |
| PCI | 538 (6%) | 244 (9%) | 187 (4%) | <0.001 |
| CABG | 65 (1%) | 22 (1%) | 26 (1%) | 0.22 |
| **Hospital length of stay (days)** | 8 (5, 12) | 8 (5, 12) | 8 (5, 12) | 0.043 |
| **Discharge medication, n(%)** | | | | |
| ACEi/ARB | 6037 (70%) | 1841 (66%) | 3091 (61%) | <0.001 |
| Beta blockers | 6652 (77%) | 2066 (74%) | 3359 (67%) | <0.001 |
| MRAs | 5156 (60%) | 1200 (43%) | 1843 (37%) | <0.001 |
| Diuretics (all) | 7533 (87%) | 2284 (82%) | 4057 (80%) | <0.001 |
| Diuretics (loop) | 7448 (86%) | 2209 (79%) | 3829 (76%) | <0.001 |

HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure heart failure with mid-range or mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; ICU, intensive care unit; ED, emergency department; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEi, angiotensin- converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

* within 6 hours of admission

**Table 3:** Healthcare resource utilization in hospitalized heart failure patients according to left ventricular ejection fraction phenotype

| | HFrEF | HFmrEF | HFpEF | p-value |
|---|---|---|---|---|
| **N** | 8904 | 2871 | 5168 | |
| **Number of in- and out-hospital services used** | | | | <0.001 |
| 0 | 402 (5%) | 143 (5%) | 256 (5%) | |
| 1 | 2688 (30%) | 962 (34%) | 1746 (34%) | |
| 2 | 4518 (51%) | 1403 (49%) | 2665 (52%) | |
| 3 | 1296 (15%) | 363 (13%) | 501 (10%) | |
| **Number of in-hospital interventions** | | | | <0.001 |
| 0 | 8299 (93%) | 2605 (91%) | 4956 (96%) | |
| 1 | 589 (7%) | 262 (9%) | 209 (4%) | |
| 2 | 7 (<1%) | 2 (<1%) | 2 (<1%) | |
| **Number of in-hospital intravenous therapies** | | | | <0.001 |
| 0 | 763 (9%) | 268 (9%) | 488 (9%) | |
| 1 | 5505 (62%) | 1812 (63%) | 3436 (66%) | |
| 2 | 2279 (26%) | 698 (24%) | 1111 (21%) | |
| 3 | 357 (4%) | 93 (3%) | 133 (3%) | |
| **Total number of in-hospital therapies** | | | | <0.001 |
| 0 | 675 (8%) | 220 (8%) | 456 (9%) | |
| 1 | 5257 (59%) | 1719 (60%) | 3349 (65%) | |
| 2 | 2459 (28%) | 775 (27%) | 1177 (23%) | |
| ≥3 | 504 (6%) | 155 (5%) | 185 (4%) | |
| **Number of discharge medications** | | | | <0.001 |
| 0 | 119 (1%) | 63 (2%) | 163 (3%) | |
| 1 | 685 (8%) | 297 (11%) | 707 (14%) | |
| 2 | 1778 (21%) | 834 (30%) | 1615 (32%) | |
| 3 | 3001 (35%) | 982 (35%) | 1811 (36%) | |
| 4 | 3057 (35%) | 622 (22%) | 747 (15%) | |
| **Hospitalizations at 12 months** | 3219 (38%) | 1055 (38%) | 1944 (39%) | 0.410 |

In-hospital services: ED, ICU and general ward; in- and out-hospital services: ambulance transportation, ED, ICU, general ward; in-hospital interventions: PCI, CABG; in-hospital intravenous therapies: iv Inotropes, iv Vasodilators, iv Diuretics; total in-hospital therapies: PCI, CABG, iv inotropes, iv vasodilators, iv diuretics; discharge medications: ACEI/ARB/ARNI, beta-blockers, MRA, diuretics; hospitalizations at 12 months; all-cause or HF-related

**Table 4:** In-hospital and one-year outcomes of hospitalized heart failure patients according to left ventricular ejection fraction phenotype

| | **HFrEF** | **HFmrEF** | **HFpEF** | ***P-value*** |
|---|---|---|---|---|
| **N** | 8904 | 2871 | 5168 | |
| In-hospital mortality | 235 (3%) | 57 (2%) | 111 (2%) | 0.058 |
| All-cause mortality at 12 months | 1819 (22%) | 505 (18%) | 792 (16%) | <0.001 |
| CV mortality at 12 months | 1144 (14%) | 303 (11%) | 438 (9%) | <0.001 |
| All-cause hospitalization at 12 months | 3219 (38%) | 1055 (38%) | 1944 (39%) | 0.410 |
| HF hospitalization at 12 months | 2085 (25%) | 554 (20%) | 1044 (21%) | <0.001 |

HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure heart failure with mid-range or mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; CV, cardiovascular; HF, heart failure.

**Table 5:** Unadjusted and adjusted rates of 12-month post-discharge mortality in hospitalized heart failure with mid-range/mildly-reduced left ventricular ejection fraction (HFmrEF) and preserved left ventricular ejection fraction (HFpEF) compared to those with reduced left ventricular ejection fraction (HFrEF). Data expressed as HR (95%CI) p-value.

| | **HFrEF** | **HFmrEF** | **HFpEF** |
|---|---|---|---|
| **N** | 8904 | 2746 | 4951 |
| **All-cause mortality at 12 months** | | | |
| Univariable | - | 0.83 (0.75-0.92) <0.001 | 0.72 (0.65-0.77) <0.001 |
| Model 1 | - | 0.78 (0.71-0.86) <0.001 | 0.65 (0.60-0.72) <0.001 |
| Model 2 | - | 0.78 (0.59-0.71) <0.001 | 0.64 (0.59-0.87) <0.001 |
| **Cardiovascular mortality at 12 months*** | | | |
| Univariable | - | 0.80 (0.71-0.91) <0.001 | 0.63 (0.71-0.91) <0.001 |
| Model 1 | - | 0.77 (0.68-0.88) <0.001 | 0.61 (0.54-0.69) <0.001 |
| Model 2 | - | 0.80 (0.70-0.92) 0.001 | 0.63 (0.56-0.71) <0.001 |
| **Non-cardiovascular mortality at 12 months*** | | | |
| Univariable | - | 1.03 (0.80-1.34) 0.802 | 1.23 (1.00-1.40) 0.047 |
| Model 1 | - | 0.92 (0.71-1.20) 0.537 | 1.03 (0.83-1.29) 0.785 |
| Model 2 | - | 0.93 (0.71-1.20) 0.556 | 1.00 (0.80-1.26) 0.996 |

Model 1: age, sex, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, chronic renal disease, coronary artery disease.
Model 2: model1 plus angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, mineralocorticoid receptor antagonists, diuretics, race, HF diagnosis (new-onset vs DCHF), number of in-hospital services used and mode of transport to hospital.
*competing risk: cardiovascular/unknown for non-cardiovascular mortality; non-cardiovascular/unknown for cardiovascular mortality

**Central illustration**

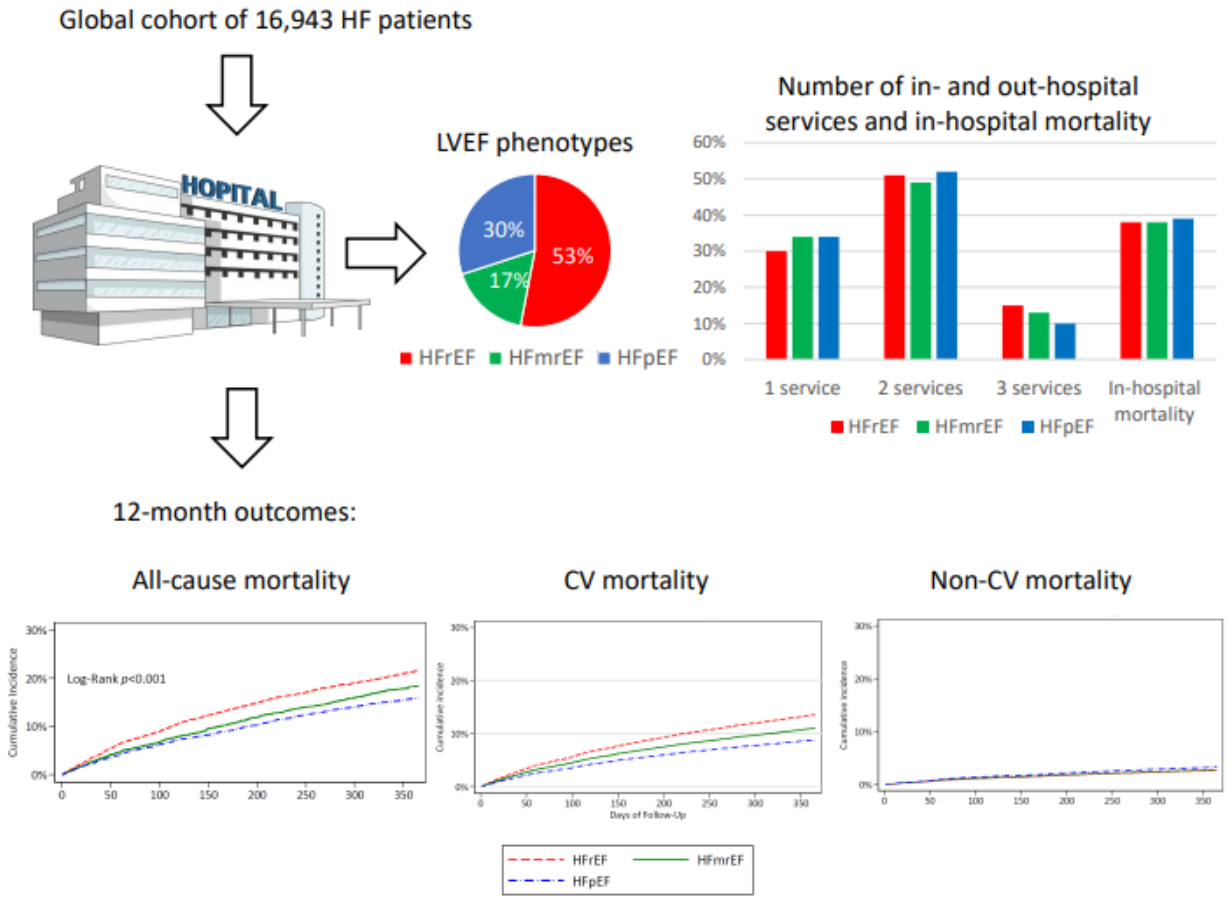
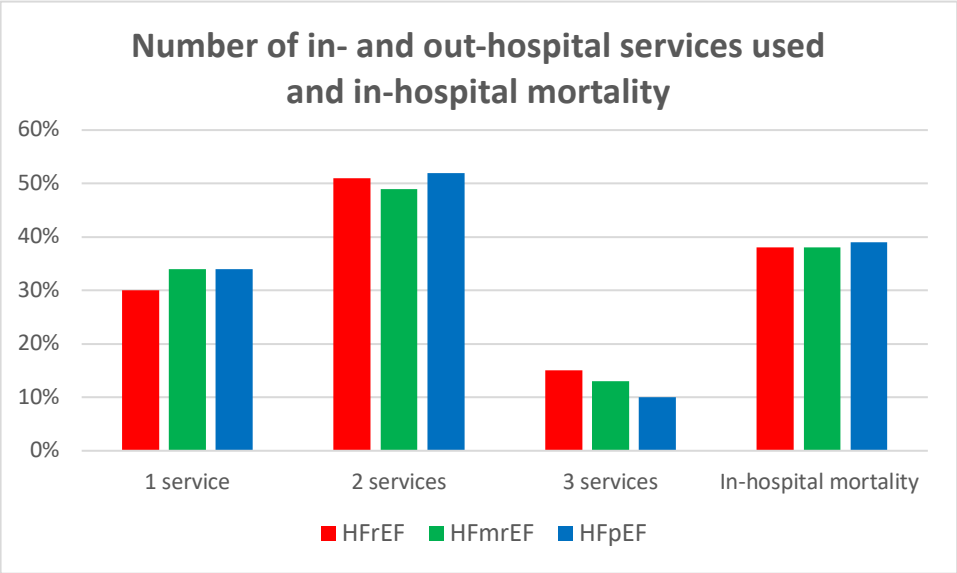


**Figure 1**


Cumulative Mortality
Stratified to heart failure subtype
Cumulative Incidence
30%
20%
10%
0%
Log-Rank p<0.001
0
50
100
150
200
250
300
350
Year of Follow-Up
Number at risk
HFrEF 8448 7995 7693 7405 7178 6987 6820 6642
HFmrEF 2746 2633 2563 2484 2414 2354 2300 2246
HFpEF 4951 4777 4643 4543 4437 4328 4249 4171
HFrEF
HFmrEF
HFpEF
Cumulative CV Mortality
Stratified to heart failure subtype
Cumulative incidence
30%
20%
10%
0%
0
50
100
150
200
250
300
350
Days of Follow-Up
HFrEF
HFmrEF
HFpEF
Cumulative Non-CV Mortality
Stratified to heart failure subtype
Cumulative incidence
30%
20%
10%
0%
0
50
100
150
200
250
300
350
Days of Follow-Up
HFrEF
HFmrEF
HFpEF

**Figure 2**


Number of in- and out-hospital services used and in-hospital mortality
60%
50%
40%
30%
20%
10%
0%
1 service
2 services
3 services
In-hospital mortality
HFrEF
HFmrEF
HFpEF