

Heart failure patients with improved ejection fraction: insights from the MECKI Score database.

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Abstract

Aims: Improvement of left ventricular ejection fraction is a major goal of heart failure (HF) treatment.

However, data on clinical characteristics, exercise performance and prognosis in HF patients who improved ejection fraction (HFimpEF) are scarce.

The study aimed to determine whether HFimpEF patients have a distinct clinical phenotype, biology and prognosis than HF patients with persistently reduced ejection fraction (pHFrEF).

Methods and Results: 7948 patients enrolled in the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score database were evaluated (median follow-up of 1490 days). We analyzed clinical, laboratory, ECG, echocardiographic, exercise, and survival data from HFimpEF (n=1504) and pHFrEF (n=6017) patients. The primary endpoint of the study was the composite of cardiovascular death, left ventricular assist device implantation, and urgent heart transplantation.

HFimpEF patients had lower HF severity: LVEF 44.0[41.0-47.0] vs. 29.7[24.1-34.5]%, BNP 122[65-296] vs. 373[152-888] pg/mL, hemoglobin 13.5[12.2-14.6] vs. 13.7[12.5-14.7] g/dL, renal function by MDRD 72.0[56.7- 89.3] vs. 70.4[54.5-85.3] mL/min, peakVO₂ 62.2[50.7-74.1] vs. 52.6[41.8-64.3]%pred, VE/VCO₂ slope 30.0[26.9-34.4] vs. 32.1[28.0-38.0] in HFimpEF and pHFrEF, respectively (p<0.001 for all). Cardiovascular mortality rates were 26.6 and 46.9 per 1000 person-years for HFimpEF and pHFrEF, respectively (p<0.001). Kaplan–Meier analysis showed that HFimpEF had better a long-term prognosis compared with pHFrEF patients. After adjustment for variables differentiating HFimpEF from pHFrEF, except echocardiographic parameters, the Kaplan–Meier curves showed the same prognosis.

Conclusions: HFimpEF represents a peculiar group of HF patients whose clinical, laboratory, ECG, echocardiographic, and exercise characteristics parallel the recovery of systolic function. Nonetheless, these patients remain at risk for adverse outcome.

Keywords: Heart failure; left ventricular ejection fraction; heart failure with improved ejection fraction; prognosis; outcomes; cardiopulmonary exercise test.

Abbreviations and acronyms:

ACEi = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor/neprilysin inhibitor
BNP = Brain natriuretic peptide
CO₂ = carbon dioxide
CPET = cardiopulmonary exercise test
CRT = cardiac resynchronization therapy
CV = cardiovascular
ECG = electrocardiogram
EOV = exercise oscillatory ventilation
HB1Ac = hemoglobin A1c
HF = heart failure
HFimpEF = heart failure with improved ejection fraction
HFrEF = heart failure with reduced ejection fraction
HTX = heart transplantation
ICD = implantable cardioverter-defibrillator
LBB = left bundle branch
LV = left ventricle
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
LVeDV = left ventricle end-diastolic volume
LVeSV = left ventricle end-systolic volume
MDRD = renal function expressed as Modification of Diet in Renal Disease
MECKI = Metabolic Exercise test data combined with Cardiac and Kidney Indexes
MRA = mineralocorticoid receptor antagonists
NYHA = New York Heart Association
NT-proBNP = N-terminal pro-B-type natriuretic peptide
PAPs = pulmonary arterial pressures
pHFrEF = heart failure with persistently reduced ejection fraction
VCO₂ = carbon dioxide consumption
VE = ventilation
 \sqrt{E}/VCO_2 slope = ventilation/carbon dioxide production slope
VO₂ = oxygen uptake

Introduction

In chronic heart failure (HF), left ventricular ejection fraction (LVEF) is the most commonly used parameter for risk stratification and setting treatment options. However, LVEF can change dynamically and either worsen with disease progression or improve with appropriate HF treatment (1). The phenotype of HF patients with reduced ejection fraction (HFrEF, LVEF < 40%) whose LVEF improved to 40-50% (HFimpEF) has been reported since many years (2) and was recently reassessed in detail (3). Although the incidence of HFimpEF patients is increasing with the progressive improvement of HFrEF treatments, little is known about their clinical, laboratory, electrocardiographic (ECG), echocardiographic and exercise performance characteristics, and how these data influence the outcome. The clinical course of patients with HFimpEF and patients with persistent heart failure with reduced ejection fraction (pHFrEF) may indeed differ, but only few studies have specifically examined these differences. To better characterize HFimpEF patients and answer some of these questions, we analyzed data from patients enrolled in the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score database (4).

Methods

We retrospectively analyzed data from a cohort of 7948 HF patients, enrolled between 1993 and January 2022 and followed up prospectively in 26 highly experienced Institutions within Italy participating in the MECKI score research group database (5). Inclusion criteria were HF patients in New York Heart Association (NYHA) functional classes I through IV, stages B and C of American College of Cardiology/American Heart Association classification, history of HFrEF (LVEF < 40%) or LVEF < 40% at the time of enrollment, unchanged HF medications for at least 3 months, ability to perform cardiopulmonary exercise test (CPET), no major cardiovascular (CV) treatment or interventions planned. Exclusion criteria were a history of pulmonary embolism, moderate to severe aortic and mitral stenosis, pericardial disease, severe obstructive pulmonary disease, exercise-induced angina and significant ECG alterations, or the presence of any clinical comorbidities affecting

exercise capacity (4, 5). The MECKI score was calculated using the formula reported by Agostoni et colleagues (4). Variables included in the MECKI score calculation were: LVEF, hemoglobin, sodium, kidney function by MDRD formula, peak VO_2 (% predicted) and VE/VCO_2 slope. The primary endpoint of the study was the composite of CV death, left ventricular assist device (LVAD) implantation, and urgent heart transplantation (HTX).

HF patients were grouped as pHFREF patients, i.e. $\text{LVEF} < 40\%$, and HFimpEF patients, i.e. LVEF between 40 and 50% (Figure 1). To identify HFimpEF patients we applied the definition recently published by the 2022 AHA/ACC/HFSA guidelines for the management of HF, which consider HFimpEF patients as those who have previous $\text{LVEF} \leq 40\%$ and a follow-up measurement of $\text{LVEF} > 40\%$ (6). However, for the purpose of this study we excluded patients with $\text{LVEF} > 50\%$ ($n = 403$ in the MECKI score data base) since those patients with a major recovery likely have a different phenotype.

The two groups were compared considering demographic, biochemical, ECG, echocardiographic and CPET data at the time of enrollment which were available in the MECKI score database. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) formula: $186.3 * (\text{creatinine})^{-1.154} * (\text{age})^{-0.203} * 0.75$ for women (7, 8). Echocardiography was used to measure left ventricular end-systolic (LVEsV) and end-diastolic volumes (LVEDV), and LVEF (Simpson rule). CPET was performed as previously described (4, 9). Briefly, all CPETs were performed using either an electronically braked cycle-ergometer or a treadmill; for a proper comparison (10) oxygen uptake (VO_2) data measured on the treadmill were reduced by 10% (11). A ramp protocol and a modified Bruce protocol were applied in CPET with cycle-ergometer and treadmill, respectively. The exercise protocol was set to achieve peak exercise in approximately 10 min (12). If no clinical events occurred, CPET was interrupted when patients indicated that they had reached maximal effort. We performed breath-by-breath analysis of expiratory gases and ventilation. Anaerobic threshold was measured by V-slope analysis of VO_2 and carbon dioxide consumption (VCO_2), and confirmed by ventilatory equivalents and end-tidal pressures of carbon dioxide and oxygen (4).

Patient follow-up and data management procedures were performed as previously described (4, 5). In brief, follow-up was performed according to the local HF program, and ended with the last clinical evaluation or with the patient's death, LVAD implantation or HTX. If a patient died outside the hospital where he or she was followed up, the medical records of this event were asked to the family and reviewed, and the reported cause of death, if available, was considered and included in the dataset according to the study outcomes.

Statistical analysis.

Categorical variables are presented as proportions and continuous variables as median (interquartile range) as appropriate. Between groups comparison was done by Mann–Whitney U test or Chi squared test respectively. Survival analysis is evaluated by Cox regression model, adjusting for those confounders which are known to have an influence on HF survival, such as gender, age, weight, height, NYHA class, systolic and diastolic blood pressure, heart rate, QRS length, atrial fibrillation, MDRD, hemoglobin, sodium and potassium, and exercise parameters including peakVO₂, peak heart rate during exercise, ventilation (VE), workload, and VE/VCO₂ slope. Considering the two population groups were divided according to LVEF, the latter and left ventricular volumes were excluded from the adjustment analysis. Survival is also reported by the Kaplan-Meier method (unadjusted and adjusted curves), and the log-rank test is used for comparison. A p-value <0.05 was used to define statistical significance. All statistical analyzes were performed using SAS statistical package v. 9.4 (SAS Institute Inc, Cary, NC).

The study complies with the Declaration of Helsinki, and it was approved by the Ethics Committee of Centro Cardiologico Monzino, IRCCS (Protocol number CE n. CCM 04_21 PA). All patients signed an informed consent form at the time of enrollment.

Results

Among the 7948 HF patients enrolled in the MECKI score database, all with or history of HFrEF (LVEF<40%), 403 were excluded from the present analysis having at recruitment a LVEF >50%, and 24 were excluded because the time when LVEF was obtained was undefined. Of the remaining

patients, 6017 have pHFrEF, i.e. LVEF <40%, and 1504 HFimpEF i.e. LVEF ranging between 40 and 50% (Figure 1). Of the 7521 analyzed patients 293 performed a treadmill CPET and the remaining 7298 a cycloergometer CPET.

Demographic and clinical characteristics

Demographic, ECG, echocardiographic, laboratory, and treatment data of HFimpEF and pHFrEF patients are reported in Table 1. In the overall population, HF etiology was 43.9% ischemic and 39.3% idiopathic, with the HFimpEF population having a higher prevalence of HF of non-ischemic origin. Compared to pHFrEF, HFimpEF: (i) were slightly older and were more often women with a lower prevalence of diabetes; (ii) were more likely to have higher blood pressure but less likely to have coronary artery disease; (iii) had slightly better renal function (median MDRD 72.0 [56.7-89.3] mL/min), higher levels of hemoglobin, and, if diabetic, had a better glycemic control as defined by lower Hb1Ac; (iv) were more likely to have NYHA functional class I-II (82.6%) and an overall lower HF severity as suggested by lower BNP or NT-proBNP levels; all p-values <0.05. As regards ECG findings, the heart rate was lower, the QRS average duration was shorter, and left bundle branch (LBB) block less frequent in HFimpEF patients. On echocardiography, left ventricular (LV) volumes were smaller both in end-diastole and in end-systole, and pulmonary arterial pressures (PAPs) lower; all p-values <0.001.

Participants with pHFrEF were more likely to be treated at baseline with β -blockers, mineralocorticoid receptor antagonists (MRA), digitalis, amiodarone, diuretics, as well as implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT). Conversely, the proportion of patients who were on angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or angiotensin receptor/neprilysin inhibitors (ARNI), were similar in the two groups.

Cardiopulmonary exercise test

Exercise capacity was less compromised in HFimpEF patients (Table 2). Indeed HFimpEF patients reached a higher peak VO_2 1190 [IQR 917-1540] mL/min vs. 1070 [825-1370] mL/min, 15.5 [12.2-

19.3] ml/min/kg vs. 14.0 [11.3-17.2] ml/min/kg, and 62.2 [50.7-74.1] vs. 52.6 [41.8-64.3] % of the predicted value, in HFimpEF and pHFrEF, respectively; while VE/VCO₂ slope was lower 30.0 [26.9-34.4] in HFimpEF compared to 32.1 [28.0-38.0] in pHFrEF reflecting a beneficial increase in ventilation in response to CO₂ production ($p < 0.001$ for all variables). Similarly, the anaerobic threshold was reached at a significantly higher workload and VO₂ in HFimpEF patients. Moreover, exercise oscillatory ventilation (EOV) was observed in 17.5% and 13.9% in patients with pHFrEF and HFimpEF ($p < 0.01$), respectively. Similarly, MECKI score, which is considered among the most accurate HF predictor (13), was 7.18 [3.41-14.7] % in HFimpEF and 1.84 [0.99-3.27, $p < 0.001$] % in pHFrEF, respectively.

Clinical outcomes

Over a median follow-up of 1490 [IQR 647-2740] days, 2356 patients reached the study endpoint (HFimpEF: $n = 222$, 25.4%; pHFrEF: $n = 1421$, 32.8%; $p < 0.001$). The total mortality rate was 40.3 and 63.5 deaths * 1.000 individuals / year in HFimpEF and pHFrEF, respectively ($p < 0.001$, Table 3). Hazard ratio for the primary endpoint obtained from multivariable regression analysis is reported in Table 4. Survival did not vary between pHFrEF and HFimpEF after adjustment for the analyzed confounders (HR 0.881, CI 0.727-1.068; $p = 0.1977$). In details a significant hazard ratio indicates that study variables, such as gender ($p < 0.001$), weight ($p = 0.0305$), NYHA class ($p < 0.001$), systolic and diastolic blood pressure ($p < 0.05$ and $p < 0.001$ respectively), QRS duration ($p = 0.0231$), peak VO₂ ($p < 0.001$) and VE/VCO₂ slope ($p = 0.0015$), MDRD ($p < 0.001$), and Na⁺ ($p < 0.001$) and K⁺ ($p = 0.0493$) serum concentration, maintain their prognostic role even after adjustment for the other variables including the HF group.

Figure 2 shows the Kaplan–Meier survival curves for the two groups. Ten-year survival by Kaplan–Meier analysis showed that pHFrEF is associated with a worse survival (Figure 2, upper panel). After adjusting Kaplan–Meier survival curves for clinical characteristics (gender, age, weight, height, NYHA class, systolic and diastolic blood pressure), ECG data (heart rate, QRS length, atrial fibrillation), laboratory data (MDRD, hemoglobin, sodium and potassium), and exercise parameters

(peakVO₂, heart rate, ventilation (VE), workload, and VE/VCO₂ slope), the two curves superimpose showing the same prognosis (Figure 2, lower panel). Of note, LVEF and left ventricular volumes were not included in the adjustment analysis.

Discussion

Our study shows that HFimpEF are frequently observed in clinical practice, accounting for nearly 1 in 5 HFrefEF patients. HFimpEF patients have a better prognosis and lower disease severity compared to pHFrefEF patients (central illustration).

HFimpEF represents a peculiar group of patients whose clinical and laboratory data evolve in parallel with the recovery of systolic function. Nevertheless, we have shown that these patients remain at substantial risk for adverse outcome, reinforcing the notion that this phenotype does not imply "recovery" or normalization of LV function and that they are likely to benefit from careful follow-up and therapeutic strategies that improve outcomes, as recommended in the guidelines (6).

Consistent with the findings of other studies (1), HFimpEF patients represent a clinically distinct group compared with pHFrefEF, as evidenced by the striking differences in baseline characteristics.

In particular, a nonischemic etiology, likely mediated by the higher prevalence of female gender, was reported more frequently in HFimpEF (14) and may explain the lower incidence of CV death in this population. Similarly, higher blood pressure was more common in HFimpEF patients, suggesting a less severe HF clinical presentation and a better CV prognosis, which was confirmed by lower NYHA classes and natriuretic peptide levels. In parallel, hemoglobin concentration was also higher and renal function was better. The pattern of positive ventricular remodeling at HFimpEF was characterized by less dilated left ventricles associated with a shorter QRS interval and less frequent LBB. Finally, improvement in LVEF was associated with improvement in exercise capacity, including VO₂ at peak exercise and at the anaerobic threshold, ventilation efficiency during exercise, and lower incidence of EOV. It must be underlined that among MECKI score variables those with the strongest prognostic power are those derived from CPET, peak VO₂

and VE/VCO₂ slope (15). Moreover, when prognosis evaluation is repeated in HF patients follow-up, CPET derived parameters changes are those who drive the MECKI score capacity to pick differences in prognosis (16)

The lower severity of the disease is likely the cause of the observed difference between the two HF groups in diuretics, β -blockers, MRA, digitalis, and amiodarone.

Data towards an overall clinical, laboratory and survival improvement in HFimpEF compared to pHFrEF introduced the concept that the evolution of HF recognizes a holistic pattern in which the disease is a complex system and many elements should be considered to evaluate the overall picture (16). Accordingly, although LVEF *per se* remains a key measure for identifying groups of patients in need of specific HF treatment according to the guidelines or for stratifying prognosis, it is only a clinical marker indicating the overall condition of the patient. When the survival analysis is adjusted for the main distinguishing variables between HFimpEF and pHFrEF, but LVEF and LV volumes, the two curves overlap and show similar survival in pHFrEF and HFimpEF patients (Table 4 and Figure 2, bottom panel) (16). Of note, even after adjustment for the study variables but LVEF and LV volumes, gender, weight, NYHA class, blood pressure, QRS duration, peakVO₂, VE/VCO₂ slope, MDRD and serum electrolytes maintained an independent prognostic role. Therefore, in clinical practice, more attention should be paid to the assessment of the overall characteristics of the HF patient despite the LVEF. Hopefully, the relatively new HF treatment such as ARNI and SGLT2i, that are agnostic to the LVEF and go beyond the conventionally created thresholds of LVEF, will change the treatment paradigm and limit the importance of LVEF for the medical management of HF in the near future. Our findings are consistent with this concept.

The overall mortality rate and the CV mortality rate (Table 3) were significantly lower in HFimpEF compared with pHFrEF. Regardless of the causes of recovery of systolic function, the group of HFimpEF patients is characterized by lower mortality compared with the group of patients with pHFrEF (Figure 2, top panel). In fact, despite the better outcome and longer survival, patients with

HFimpEF are still at risk of later death from HF and should therefore not be considered cured of their disease. Indeed, the annual mortality rate for HFimpEF is still $26.6 * 1000$ individuals / year.

Limitations

This study has several limitations that must be underlined. First, it is an observational study, although it is based on an extensive database with a long follow-up period conducted by highly experienced HF centers. Second, the MECKI score database enrolled patients with a history of HFrEF or LVEF<40% at the time of enrollment (4). Baseline characteristics were collected at the time of the enrollment which does not necessarily coincide with the time of the first diagnosis of HF in the specific patient with pHFrEF and certainly not the first diagnosis in HFimpEF cases. Therefore, patients' characteristics at the time of the first HFrEF diagnosis are missed. In the HFimpEF population, the level of LVEF prior to the improvement was not recorded, so the entity of LVEF recovery is unknown. Similarly, we do not know whether HFimpEF patients continued to improve over time or whether the measured LVEF was only a transient improvement. Third, to identify HFimpEF patients we applied the recent definition of HFimpEF as published by the 2022 AHA/ACC/HFSA guidelines for the management of HF (6).

However, we excluded patients with LVEF>50% as their full recovery highlights a likely different phenotype. Of note, the inclusion and exclusion criteria of the MECKI score database were defined in 2012 along with the first data publication (4) well before any definition of HFimpEF. Fourth, clinical, laboratory, echocardiographic, and CPET data changes and treatment strategies during follow-up are unknown. Drug dosages in the two groups have not been collected. Fifth, in addition to NYHA classification, we did not consider findings such as history of HF hospitalization as surrogates for clinical severity. Sixth, in the MECKI score database, we do not know the causes of cardiovascular death and, in particular, how many patients died of sudden death. Finally, although various LVEF parameters have been used to define HFimpEF (1, 2), for this analysis we used the definition of HFimpEF with the cut-off point of LVEF > 40%, which is consistent with the current heart failure management guidelines (1).

Conclusions

In conclusion, our data support HFimpEF as a stratum of HF with a more favorable outcome. HFimpEF occurs approximately in 20% of patients with HFrEF. Patients have a lower prevalence of ischemic heart disease, a less severe hemodynamic, biomarker, and neurohormonal profile, and better exercise performance. Nonetheless, these patients remain at risk for adverse outcome, underscoring the notion that this phenotype does not imply “recovery” or normalization of LV function, and that patients benefit from careful follow-up and therapeutic strategies to improve outcomes.

Author contribution: PA and FRP contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. PA, FRP and ES drafted the manuscript. MP critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figure title and legends

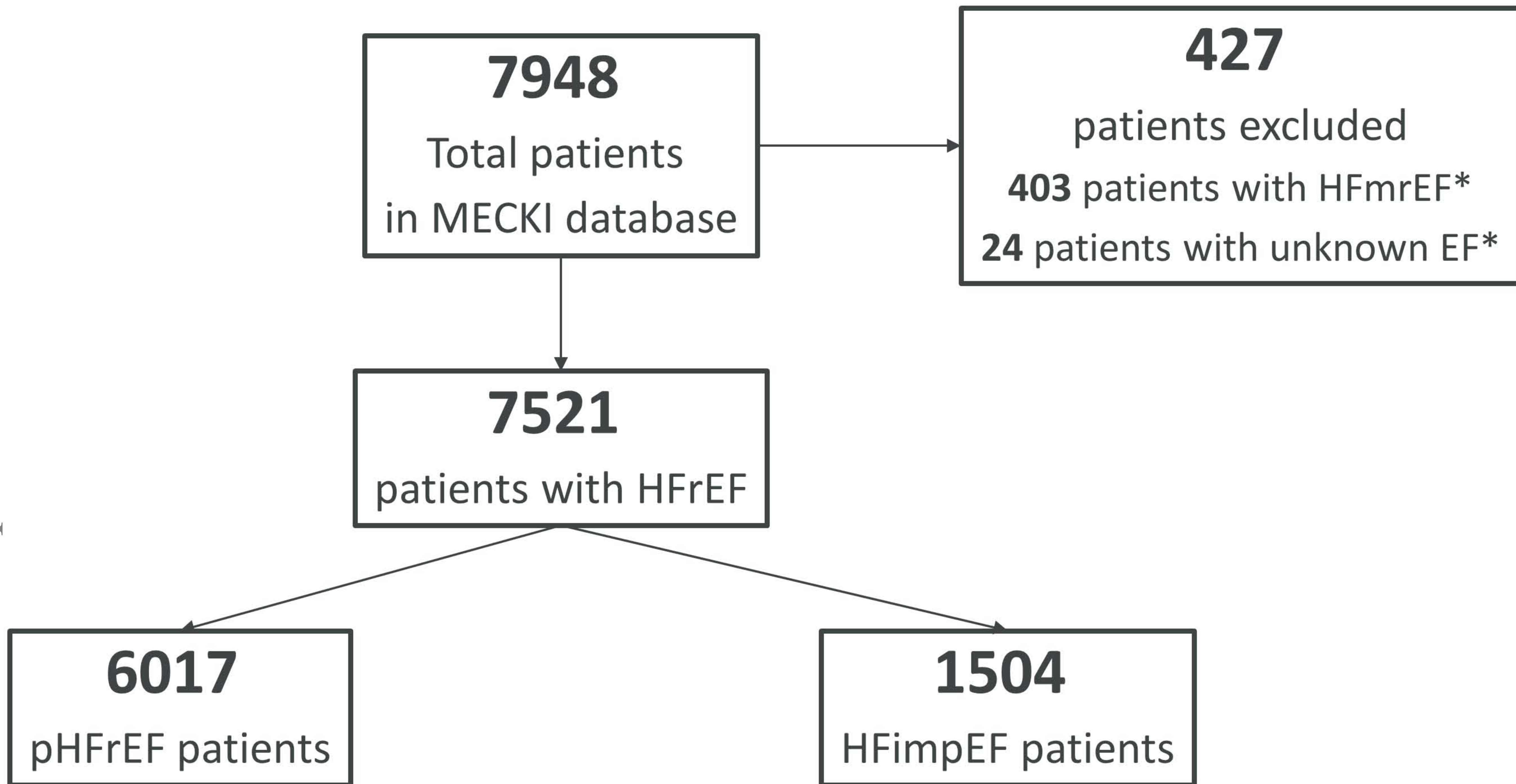
Figure1 – Study population flow chart.

Figure 2 – Kaplan Mayer curves built considering the composite endpoint of cardiovascular death, urgent heart transplant (HTX) and left ventricular assist device (LVAD) implantation.

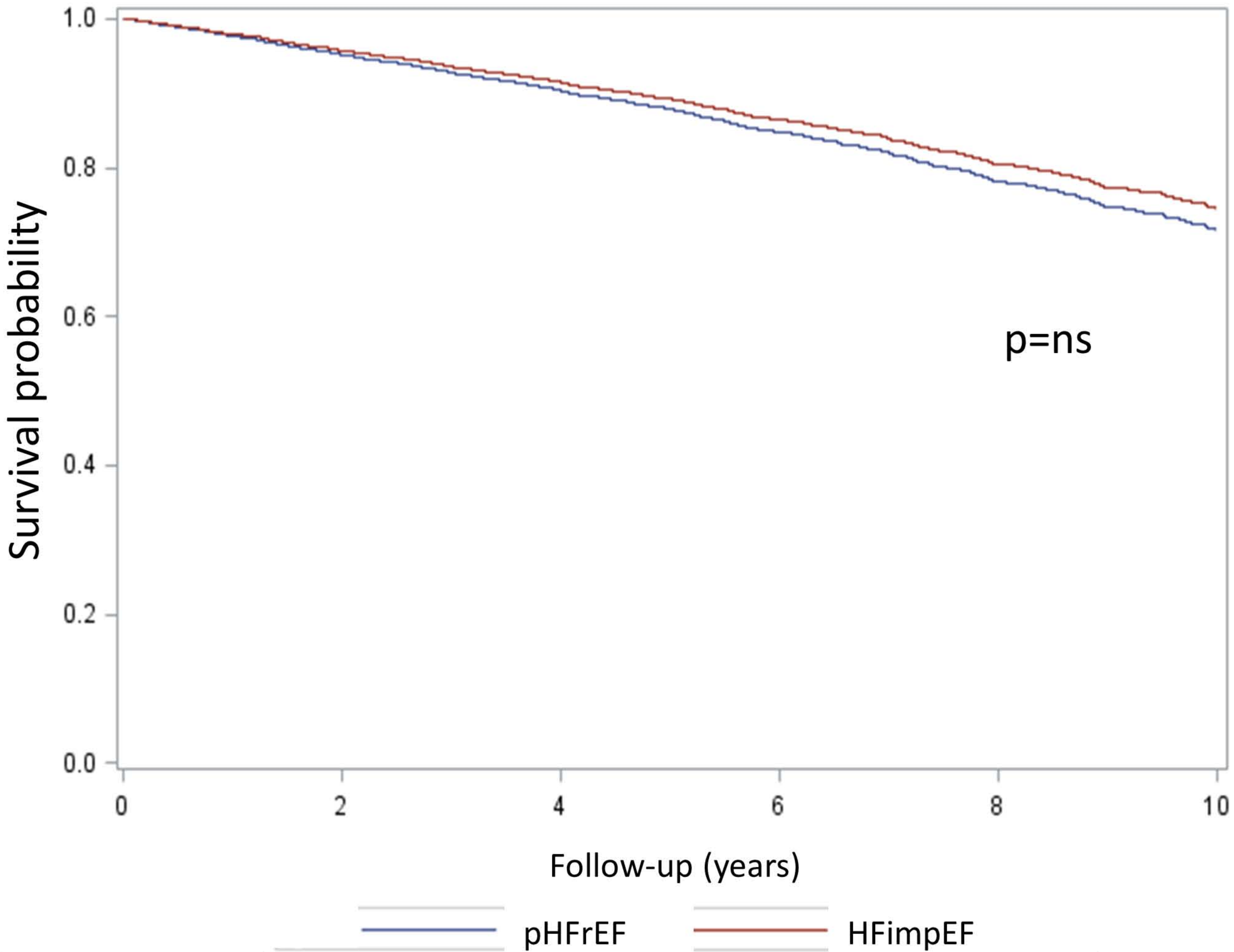
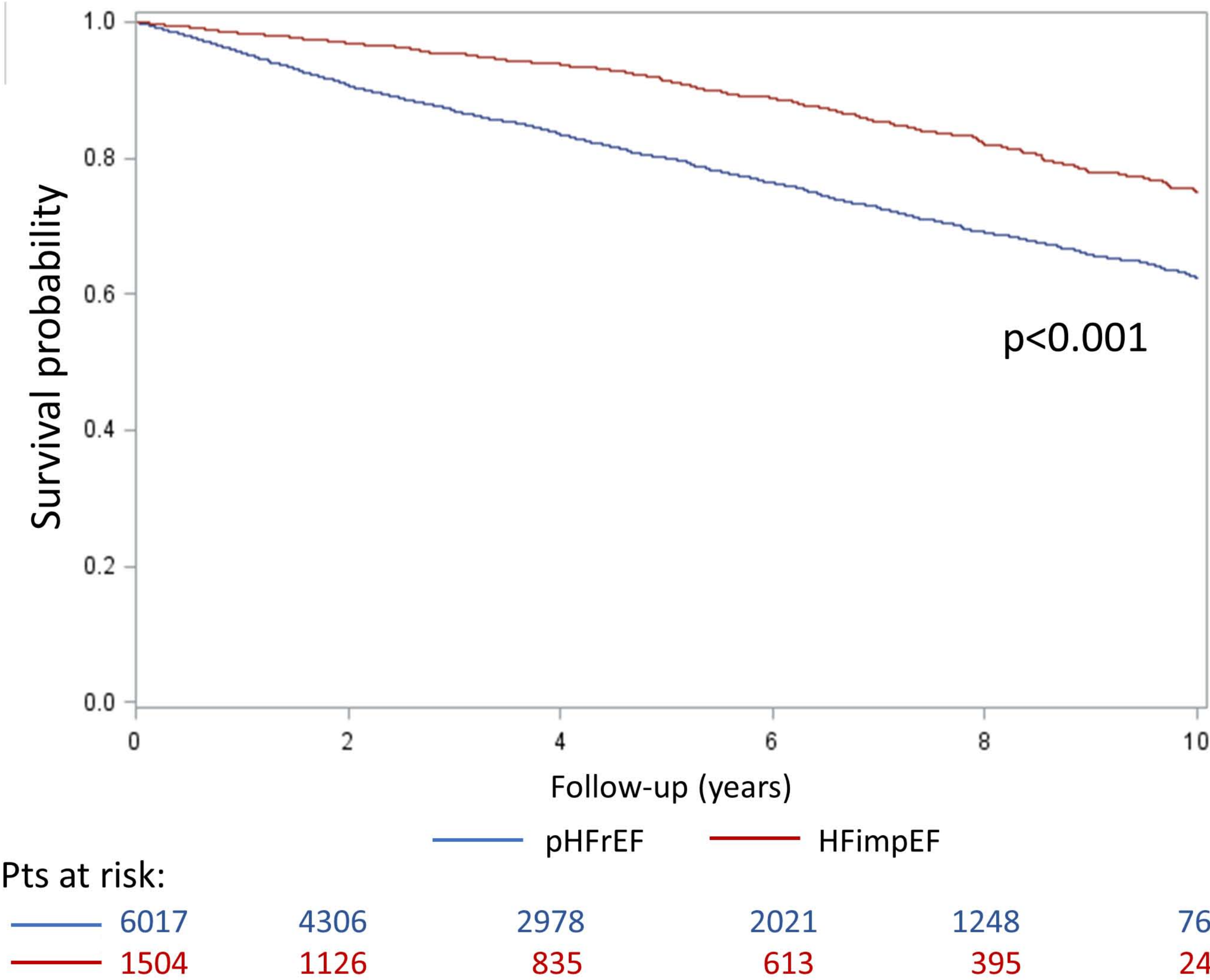
Legend: upper panel non adjusted survival; lower panel adjusted survival. Adjustment was done considering clinical characteristics (gender, age, weight, height, NYHA class, systolic and diastolic blood pressure), ECG data (heart rate, QRS length, atrial fibrillation), exercise parameters (peakVO₂, heart rate, ventilation (VE), workload, and VE/VCO₂ slope), laboratory data (MDRD, hemoglobin, sodium and potassium) data. Of note, left ventricular ejection fraction (LVEF) and left ventricular volumes were not included in the adjustment analysis.

Graphical abstract – Characteristics of HFimpEF patients and outcome comparison with pHFrEF.

Legend: arrows indicate a higher number of elements / level in HFimpEF compared to the comparison population (pHFrEF). CPET = cardiopulmonary exercise test; CV = cardiovascular; EOv = exercise oscillatory ventilation; MECKI = Metabolic Exercise Cardiac Kidney Indexes; LBB = left bundle branch block; LVeSV = left ventricular end-systolic volume; LVeDV = left ventricular end-diastolic volume; NYHA = New York Heart Association; PAPs = pulmonary arterial pressures; VCO₂ = carbon dioxide consumption; VE = ventilation; VO₂ = oxygen uptake. [#]CV mortality is composite endpoint for CV mortality+ urgent transplant + LVAD implantation; * *events * 1000 person /year*.



**at the time of enrollment*



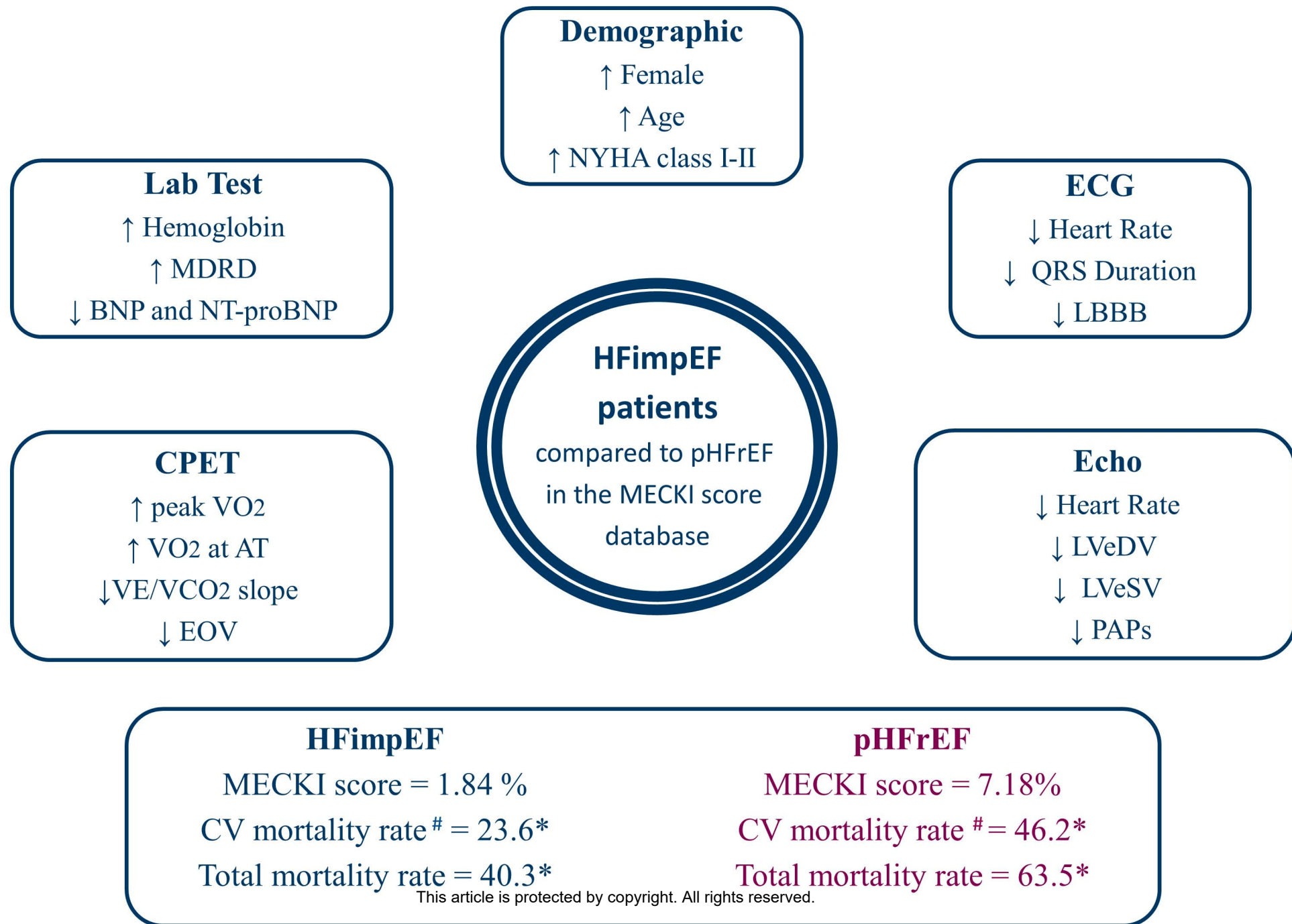


Table 1. Patients' demographic, laboratory, electrocardiographic, echocardiographic and treatment data.

	All (n=7521)	HFimpEF (n=1504)	pHFrEF (n=6017)	p value
Demographic and Characteristics				
Female (n, %)	1295 (17.2)	356 (23.7)	939 (15.6)	<0.001
Age (years)	62.0 [53.0, 71.0]	64.0 [54.0, 73.0]	62.0 [53.0, 70.0]	<0.001
Weight (kg)	76.0 [68.0, 86.0]	77.0 [68.0, 86.0]	76.0 [67.3, 86.0]	0.368
Height (cm)	170 [165, 175]	170 [165, 175]	170 [165, 175]	0.371
BMI (kg/m ²)	26.2 [23.8, 29.1]	26.4 [24.1, 29.3]	26.2 [23.8, 29.1]	0.154
NYHA Class (n, %)				
NYHA 1-2	5297 (70.4)	1243 (82.6)	4054 (67.4)	<0.001
NYHA 3-4	2177 (28.9)	256 (17.0)	1921 (31.9)	<0.001
Missing	47 (0.6)	5 (0.3)	42 (0.7)	
HF etiology (n, %)				
Ischemic	3233 (43.0)	591 (39.3)	2642 (43.9)	<0.001
Primitive	2998 (39.9)	552 (36.7)	2446 (40.7)	
Valvular	259 (3.4)	97 (6.4)	162 (2.7)	
Other	501 (6.7)	203 (13.5)	298 (5.0)	
Missing	530 (7.0)	61 (4.1)	469 (7.8)	
Systolic Blood Pressure (mmHg)	120 [105, 130]	120 [110, 130]	115 [100, 130]	<0.001
Diastolic Blood Pressure (mmHg)	70.0 [65.0, 80.0]	75.0 [70.0, 80.0]	70.0 [65.0, 80.0]	<0.001
Diabetes (n, %)	1116 (14.8)	239 (15.9)	877 (14.6)	0.033
Laboratory Tests				
Hemoglobin (g/dL)	13.6 [12.4, 14.7]	13.5 [12.2, 14.6]	13.7 [12.5, 14.7]	<0.001
Na ⁺ (mmol/L)	140 [138, 141]	140 [138, 141]	140 [138, 141]	0.082
K ⁺ (mmol/L)	4.30 [4.00, 4.60]	4.25 [3.97, 4.58]	4.30 [4.00, 4.60]	0.044
MDRD (mL/min)	70.8 [55.0, 86.1]	72.0 [56.7, 89.3]	70.4 [54.5, 85.3]	<0.001
BNP (pg/mL)	286 [110, 712]	122 [65, 296]	373 [152, 888]	<0.001
NT-proBNP (pg/mL)	1020 [466, 2360]	461 [144, 989]	1150 [517, 2500]	<0.001
Lymphocytes (%)	27.9 [21.6, 34.0]	30.0 [23.0, 36.0]	27.0 [21.0, 33.2]	<0.001
Uric Acid (mg/dL)	6.10 [5.00, 7.60]	6.00 [5.00, 7.00]	6.30 [5.10, 7.70]	<0.001
Cholesterol (mg/L)	175 [147, 202]	179 [155, 202]	174 [145, 202]	<0.001
HbA1c (%)	6.10 [5.00, 7.00]	5.50 [4.60, 6.70]	6.40 [5.60, 7.20]	<0.001
ECG variables				
Hear Rate (bpm)	69.0 [61.0, 78.0]	67.0 [60.0, 75.0]	70.0 [62.0, 78.0]	<0.001
QRS Duration (ms)	115 [90.0, 140]	100 [85.0, 130]	120 [95.0, 145]	<0.001
Left Bundle Branch Block (n, %)	1654 (22.0)	243 (16.2)	1411 (23.5)	<0.001
Right Bundle Branch Block (n, %)	414 (5.5)	98 (6.5)	316 (5.3)	0.143
Left anterior hemiblock (n, %)	957 (12.7)	229 (15.2)	728 (12.1)	0.022
Atrial Fibrillation (n, %)	1310 (17.4)	286 (19.0)	1024 (17.0)	0.07
Echocardiographic Variables				
LVEF (%)	32.0 [25.0, 38.0]	44.0 [41.0, 47.0]	29.7 [24.1, 34.5]	<0.001
LVeDV (ml)	175 [133, 221]	133 [108, 166]	186 [146, 233]	<0.001
LVeSV (ml)	116 [83.3, 158]	74.0 [59.0, 94.0]	130 [98.0, 171]	<0.001

PAPs (mmHg)	35.0 [28.0, 44.0]	30.0 [25.0, 37.0]	35.0 [29.0, 45.0]	<0.001
Treatments				
ACEi/ARB/ARNI (n, %)	6759 (89.9)	1336 (88.8)	5423 (90.1)	0.0714
B-blocker (n, %)	6566 (87.3)	1230 (81.8)	5336 (88.7)	<0.001
MRA (n, %)	3959 (52.6)	567 (37.7)	3392 (56.4)	<0.001
Diuretics (n, %)	5962 (79.3)	995 (66.2)	4967 (82.5)	<0.001
Digitalis (n, %)	1387 (18.4)	188 (12.5)	1199 (19.9)	<0.001
Amiodarone (n, %)	1803 (24.0)	281 (18.7)	1522 (25.3)	<0.001
Allopurinol (n, %)	2019 (26.8)	350 (23.3)	1669 (27.7)	<0.001
Antiplatelet medication (n, %)	3946 (52.5)	816 (54.3)	3130 (52.0)	0.524
Oral anticoagulant therapy (n, %)	2346 (31.2)	430 (28.6)	1916 (31.8)	0.0034
ICD (n, %)	2623 (34.9)	214 (14.2)	2409 (40.0)	<0.001
CRT (n, %)	1115 (14.8)	85 (5.7)	1030 (17.1)	<0.001

Legend: ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; ARNI = Angiotensin Receptor Neprilysin Inhibitor; β -blockers = beta-adrenoceptor blocking agents; BMI = body mass index; BNP = brain natriuretic peptide (n = 3530); CRT =cardiac resynchronization therapy; ECG = electrocardiogram; HbA1c = Hemoglobin A1c; HF = heart failure; ICD = implantable cardioverter-defibrillator; K⁺ = potassium; LVEF = left ventricular ejection fraction; LVeSV = left ventricular end-systolic volume; LVeDV = left ventricular end-diastolic volume; Na⁺ = sodium; MRA = mineralocorticoid receptor antagonist; MDRD = modification of diet in renal disease; NYHA = New York Heart Association; NT-proBNP = N-terminal pro b-type natriuretic peptide (n=1489); PAPs= pulmonary arterial pressures; categorical variables are presented as proportions (n, %); continuous variables are reported as median [interquartile range].

Table 2. Functional evaluation of the study population by cardiopulmonary exercise test.

	All (n=7521)	HFimpEF (n=1504)	pHFrEF (n=6017)	p value
CPET Variables				
Ramp protocol (Watt/min) ^a	10.0 [10.0, 10.0]	10.0 [10.0, 10.0]	10.0 [8.00, 10.0]	<0.001
EOV (n, %)	1260 (16.8)	209 (13.9)	1051 (17.5)	0.005
Anaerobic threshold (n, %)	6034 (80.2)	1197 (79.6)	4837 (80.4)	0.554
VO ₂ at AT (mL/kg/min)	775 [608, 990]	843 [673, 1080]	758 [593, 959]	<0.001
HR at AT (bpm)	94.0 [83.0, 107]	95.0 [84.0, 109]	93.0 [82.0, 107]	0.005
Work rate at AT (watt)	49.0 [34.0, 65.0]	53.0 [40.0, 73.0]	47.0 [33.0, 61.0]	<0.001
Peak VO ₂ (mL/min)	1090 [840, 1400]	1190 [917, 1540]	1070 [825, 1370]	<0.001
Peak VO ₂ predicted (%)	54.3 [43.3, 66.7]	62.2 [50.7, 74.1]	52.6 [41.8, 64.3]	<0.001
Peak HR (bpm)	117 [101, 133]	119 [103, 138]	116 [100, 133]	<0.001
Peak work rate (watt)	80.0 [60.0, 102]	90.0 [64.0, 117]	76.0 [58.0, 100]	<0.001
VE/VCO ₂ slope	32.0 [28.0, 37.4]	30.0 [26.9, 34.4]	32.1 [28.0, 38.0]	<0.001
VO ₂ work slope (mL/min/Watt) ^a	9.60 [8.30, 11.0]	9.60 [8.10, 11.0]	9.65 [8.30, 11.0]	0.428
RR (bpm)	31.0 [27.0, 35.5]	31.0 [27.0, 36.0]	31.0 [27.0, 35.0]	0.148
Peak VE (L/min)	45.8 [36.6, 56.4]	46.5 [36.4, 58.0]	45.6 [36.6, 56.0]	0.047
RER	1.11 [1.04, 1.18]	1.11 [1.04, 1.18]	1.11 [1.05, 1.19]	0.148

Legend: AT = anaerobic threshold; CPET = cardiopulmonary exercise test; EOV = exercise oscillatory ventilation; HR = heart rate; RER= respiratory exchange ratio; RR = respiratory rate; VE = ventilation; VCO₂ =carbon dioxide consumption; VO₂ = oxygen uptake; categorical variables are presented as proportions (n, %); continuous variables are reported as median [interquartile range].

^a Bike ergometer.

Table 3. Follow up and end-points of the studied population.

	All (n=7521)	HFimpEF (n=1504)	pHFrEF (n=6017)	p value
Follow-Up (days)				
Median [Q1, Q3]	1490 [647, 2740]	1730 [729, 3010]	1440 [630, 2670]	<0.001
MECKI score (%)	5.53 [2.43, 12.5]	1.84 [0.995, 3.27]	7.18 [3.41, 14.7]	<0.001
Study endpoint (n, %)	1632 (21.7)	222 (14.8)	1410 (23.4)	<0.001
Exitus (n, %)	2119 (28.2)	371 (24.7)	11748 (29.1)	<0.001
Cause of Exitus				
CV death (n, %)	1395 (18.5)	211 (14.0)	1184 (19.7)	<0.001
nonCV death (n, %)	333 (4.4)	91 (6.0)	242 (4.0)	<0.001
Unknown (n, %)	391 (5.2)	69 (4.6)	322 (5.4)	
LVAD (n, %)	38 (0.5)	1 (0.1)	37 (0.6)	
HTX (n, %)	199 (2.6)	10 (0.7)	189 (3.1)	
Mortality Rate				
Total mortality (death * 1000 individuals / year)	58.5	40.3	63.5	<0.001
CV mortality + HTX + LVAD (events * 1000 individuals / year)	41.3	23.6	46.2	<0.001

Legend: CV = cardiovascular; HTX = Heart Transplantation; LVAD = left ventricular assist device; MECKI = Metabolic Exercise Cardiac Kidney Indexes; categorical variables are presented as proportions (n, %); continuous variables are reported as median [interquartile range].

Table 4. Cox analysis of the studied population.

	HR (95% CI)	P value
HF group	0.881 (0.727-1.068)	0.1977
Gender	2.421 (1.915-3.061)	<.0001
Age	1.002 (0.995-1.008)	0.6328
Weight	1.007 (1.001-1.013)	0.0305
Height	1.000 (0.989-1.011)	0.9729
NYHA class	1.330 (1.188-1.488)	<.0001
Systolic blood pressure	0.994 (0.989-1.000)	0.0430
Diastolic blood pressure	0.981 (0.972-0.990)	<.0001
Heart rate	1.001 (0.996-1.007)	0.6211
QRS Duration	1.002 (1.000-1.004)	0.0231
Atrial fibrillation	1.036 (0.872-1.229)	0.6895
Peak VO₂	0.999 (0.998-0.999)	<.0001
Peak Heart Rate	0.999 (0.996-1.002)	0.5962
Peak Watt	0.997 (0.993-1.001)	0.1453
VE/VCO₂ slope	1.016 (1.006-1.026)	0.0015
Peak VE	1.007 (0.998-1.015)	0.1261
MDRD	0.992 (0.989-0.995)	<.0001
Hemoglobin	0.967 (0.927-1.009)	0.1190
Na⁺	0.957 (0.939-0.976)	<.0001
K⁺	0.874 (0.765-1.000)	0.0493

Legend: CI = confidence interval; HR = hazard ratio; HF = heart failure; K⁺ = serum potassium concentration; MDRD = modification of diet in renal disease; Na⁺ = serum sodium concentration; NYHA = New York Heart association; VCO₂ = carbon dioxide production; VE = ventilation. *Adjusted for gender, age, weight, height, NYHA class, systolic and diastolic blood pressure, heart rate, QRS length, atrial fibrillation, MDRD, hemoglobin, Na⁺ and K⁺ serum concentration, peakVO₂, peak heart rate during exercise, workload, VE/VCO₂ slope, and ventilation.