ORIGINAL RESEARCH

Noncardiac Versus Cardiac Mortality in Heart Failure With Preserved, Midrange, and Reduced Ejection Fraction

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***Background*—**A thorough analysis of noncardiac determinants of mortality in heart failure (HF) is missing. Furthermore, evidence conflicts on the outcome of patients with HF and no or mild systolic dysfunction. We aimed to investigate the prevalence of noncardiac and cardiac causes of death in a cohort of chronic HF patients, covering the whole spectrum of systolic function.

***Methods and Results*—**We enrolled 2791 stable HF patients, classified into HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [EF] <40%), HR with midrange EF (HFmrEF; left ventricular EF 41–49%), or HF with preserved EF (HFpEF; left ventricular EF ≥50%), and followed up for all-cause, cardiac, and noncardiac mortality (adjudicated as due to cancer, sepsis, respiratory disease, renal disease, or other causes). Over follow-up of 39 months, adjusted mortality was lower in HFpEF and HFmrEF versus HFrEF (hazard ratio: 0.75 [95% CI, 0.67–0.84], $P<0.001$ for HFpEF; hazard ratio: 0.78 [95% CI, 0.63–0.96], $P=0.017$ for HFmrEF). HFrEF had the highest rates of cardiac death, whereas noncardiac mortality was similar across left ventricular EF categories. Noncardiac causes accounted for 62% of deaths in HFpEF, 54% in HFmrEF and 35% in HFrEF; cancer was twice as frequent as a cause of death in HFpEF and HFmrEF versus HFrEF. Yearly rates of noncardiac death exceeded those of cardiac death since the beginning of follow-up in HFpEF and HFmrEF.

***Conclusions*—**Noncardiac death is a major determinant of outcome in stable HF, exceeding cardiac-related mortality in HFpEF and HFmrHF. Comorbidities should be regarded as main therapeutic targets and objects of dedicated quality improvement initiatives, especially in patients with no or mild systolic dysfunction. **(*J Am Heart Assoc*. 2019;8:e013441. DOI: 10.1161/JAHA.119.013441.)**

Key Words: comorbidities heart failure • heart failure • mortality • prognosis

Despite recent advances in pharmacological and non-pharmacological therapy, heart failure (HF) represents a major public health burden in Western countries. Still, data about the outcomes of HF patients are incomplete and heterogeneous. Indeed, several cohort studies have reported similar mortality in HF with reduced ejection fraction (HFrEF) and in HF with preserved ejection fraction (HFpEF),[1,2] whereas others have demonstrated a significantly worse outcome in HFrEF.[3,4] Such discrepancy may be explained by the variability in the selection of cutoffs of left ventricular ejection fraction (LVEF), in the background use of drug and device therapy with prognostic impact,[5] and in the prevalence of comorbidities, which play a major role in the pathophysiology and clinical presentation in HFpEF.[6] Furthermore, outcome assessment is influenced by clinical setting (inpatient versus outpatient), as in-hospital mortality is higher in HFrEF than in HFpEF.[1,7–9]

A novel classification of HF based on LVEF was recently proposed, identifying HF with midrange ejection fraction (LVEF 40–49%) as an intermediate category between HFrEF and HFpEF.[10] Conflicting information is available about the outcomes of patients with HFmrEF; they have been reported to be associated with a favorable risk in terms of all-cause death,[11,12] an intermediate risk between HFpEF and HFrEF,[13] or a profile similar to HFpEF or HFrEF.[14,15]

Previous data from the Framingham Heart Study have shown that cardiovascular mortality is much more frequent in HFrEF than in HFpEF,[16] and the clinical relevance of noncardiovascular death in HFpEF has been pointed out in most of large clinical trials performed in such settings.[17]

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Clinical Perspective

What Is New?

- This study provides a detailed analysis of noncardiac causes of death in patients with stable heart failure with preserved, midrange, and reduced ejection fraction.

What Are the Clinical Implications?

- Noncardiac causes of death have major prognostic relevance in subgroups of heart failure patients with preserved or mildly impaired left ventricular ejection fraction.
- Common comorbidities, such as cancer, sepsis, and respiratory or renal diseases, are significant determinants of outcome in heart failure and warrant dedicated, enhanced therapeutic effort.

Nonetheless, only limited evidence is currently available on the impact of specific comorbidities on mortality in patients with chronic HF.[18]

The aim of this study was to investigate the prevalence of cardiac and major noncardiac causes of death in a large cohort of patients with stable HF, across the whole spectrum of LV systolic function.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

All patients referred for HF management to the outpatient clinic of a single tertiary center, Fondazione Toscana Gabriele Monasterio in Pisa, Italy, were prospectively considered for enrollment from 2000 to 2016. The diagnosis of HF was determined by history, symptoms, physical examination, and biohumoral (including BNPs [B-type natriuretic peptides]) and instrumental findings for the assessment of structural myocardial involvement. Only patients with stable HF-related symptoms and pharmacological therapy for at least 1 month were included; those with acute coronary syndrome or cardiac surgery within 3 months were excluded. All patients received a complete baseline clinical, biohumoral, and echocardiographic evaluation within 3 days after enrollment. Patients were then classified into 3 categories: HFrEF (LVEF <40%), HFmrEF (LVEF 40–49%), or HFpEF (LVEF ≥50%).[10] Informed consent was obtained from each patient, and the study protocol conformed to the ethics guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

Biohumoral Assays

Blood samples were drawn at 8 AM after an overnight fasting period and a 20-minute supine rest.[19] NT-proBNP (N-terminal proBNP) was measured with the ECLIA monoclonal method using the Cobas e411 platform (Roche Diagnostics). Plasma renin activity and aldosterone were assayed using a radioimmunoassay method.[20,21] Plasma norepinephrine and epinephrine were evaluated by means of high-performance liquid chromatography using the electrochemical detector CLC 100 (Chromsystems). Assays were performed according to manufacturer instructions.

Transthoracic Echocardiography

Standard 2-dimensional transthoracic echocardiography images were obtained using a Philips IE33 ultrasound machine with X5-1 transducer (Philips Medical Systems) to assess end-systolic and end-diastolic volumes, diameters, and wall thickness, according to contemporary American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. LVEF was calculated using the biplane Simpson method.[22–24] The reading was standardized and consistent across years.

Follow-Up

After baseline assessment, follow-up was performed at our outpatient clinic every 3 to 6 months, as clinically indicated. Independent interviewers obtained data from patients, relatives, or general practitioners. The follow-up period lasted until April 2018. Information about the time and cause of death was retrieved from death certificates, postmortem reports, and family doctors. Cardiac death (including sudden cardiac death and death due to HF progression or acute myocardial infarction) and heart transplantation were considered together. Noncardiac causes of death were classified as due to cancer, sepsis, respiratory disease, and renal disease. Less frequent causes of death (eg, pulmonary embolism, stroke, major hemorrhages, liver failure, neurodegenerative disorders, diabetes mellitus, and trauma) were pooled as *other causes*.

Statistical Analysis

Statistical analysis was conducted using the IBM SPSS 25.0 program. Normal distribution was assessed through the Kolmogorov–Smirnov test; variables with normal distribution were presented as mean±SD, and variables with nonnormal distribution were presented as median and interquartile range (IQR). Differences among groups were tested using 1-way ANOVA, the Kruskal–Wallis test (for nonnormally distributed variables), or χ^2 tests, and Bonferroni correction was applied

Table 1. Baseline Characteristics of the Study Population and of Subgroups With HFrEF, HFmrEF, and HFpEF

	Whole Population (N=2791)	HFrEF (n=1539)	HFmrEF (n=623)	HFpEF (n=629)	$P_{HFrEF\ vs\ HFmrEF}$	$P_{HFrEF\ vs\ HFpEF}$	$P_{HFmrEF\ vs\ HFpEF}$	*P* Value
Clinical and biohumoral characteristics								
Age, y	69±13	68±12	69±13	71±12	0.679	<0.001*	<0.001*	<0.001*
Sex, male	1948 (70)	1174 (76)	446 (72)	328 (52)	0.023*	<0.001*	<0.001*	<0.001*
Heart rate, beats/min	74±18	76±18	74±19	71±16	0.120	<0.001*	0.134	<0.001*
Ischemic etiology	1223 (44)	730 (47)	284 (46)	209 (33)	0.246	<0.001*	0.001*	<0.001*
NYHA class III/IV	1013 (36)	626 (41)	177 (28)	208 (33)	<0.001*	<0.001*	0.017*	<0.001*
Hypertension	1649 (59)	802 (52)	393 (63)	453 (72)	<0.001*	<0.001*	0.001*	<0.001*
Dyslipidemia	1301 (47)	699 (45)	310 (50)	292 (46)	0.064	0.690	0.226	0.178
Diabetes mellitus	840 (30)	448 (29)	195 (31)	198 (31)	0.311	0.296	0.976	0.439
COPD	480 (17)	279 (18)	107 (17)	97 (15)	0.590	0.156	0.457	0.364
Prior history of cancer	197 (7.0)	109 (7.1)	50 (8.0)	38 (6.1)	0.447	0.382	0.170	0.390
Active cancer	50 (1.7)	32 (2.1)	10 (1.6)	8 (1.3)	0.469	0.205	0.620	0.404
SBP, mm Hg	123±21	120±21	128±21	128±20	<0.001*	<0.001*	0.983	<0.001*
Hemoglobin, g/dL	13.2±1.8	13.4±1.8	13.3±1.8	13.0±1.8	0.751	<0.001*	0.011*	<0.001*
eGFR, mL/min/1.73 m^2	74.7±36.9	71.2±35.5	79.5±38.7	89.1±39.5	0.002*	<0.001*	0.049*	<0.001*
CKD	1061 (38)	663 (43)	199 (32)	199 (32)	<0.001*	<0.001*	0.787	<0.001*
CRP, mg/dL	0.34 (0.13–0.90)	0.36 (0.12–0.98)	0.30 (0.13–0.75)	0.33 (0.15–0.87)	0.247	1.000	1.000	0.219
hs-Troponin T, ng/L	21.5 (12.8–40.2)	24.0 (15.3–44.0)	20.2 (11.7–37.7)	18.6 (11.0–33.9)	1.000	0.001*	0.366	0.001*
NT-proBNP, ng/L	1273 (453–3378)	1811 (770–4735)	799 (301–2266)	657 (283–1834)	<0.001*	<0.001*	1.000	<0.001*
Norepinephrine, ng/L	485 (310–725)	513 (329–782)	415 (270–638)	426 (301–606)	<0.001*	0.013*	0.719	<0.001*
Epinephrine, ng/L	29 (10–60)	31 (10–62)	28 (10–58)	23 (10–54)	0.670	0.158	1.000	0.105
PRA, ng/mL/h	1.04 (0.24–3.38)	1.39 (0.35–4.32)	0.49 (0.20–2.15)	0.58 (0.20–1.65)	<0.001*	<0.001*	1.000	<0.001*
Aldosterone, ng/L	128 (74–204)	137 (77–216)	111 (67–173)	126 (73–188)	<0.001*	0.405	0.296	<0.001*
AF	815 (29)	428 (28)	195 (31)	191 (30)	0.152	0.423	0.713	0.291
LBBB	703 (25)	557 (36)	117 (19)	51 (8)	<0.001*	<0.001*	<0.001*	<0.001*
RBBB (%)	265 (10)	154 (10)	66 (11)	50 (8)	0.742	0.156	0.142	0.270
Drug and device therapy								
BB	2361 (84.6)	1387 (90.1)	546 (87.8)	427 (67.9)	0.121	<0.001*	<0.001*	<0.001*
ACEI/ARB	2319 (83.1)	1334 (86.7)	524 (84.1)	462 (73.5)	0.121	<0.001*	<0.001*	<0.001*
MRA	1577 (56.5)	1147 (74.5)	260 (41.7)	172 (27.4)	<0.001*	<0.001*	<0.001*	<0.001*
Diuretics	2180 (78.1)	1333 (86.6)	424 (68.0)	423 (67.3)	<0.001*	<0.001*	0.790	<0.001*
ICD	410 (14.7)	437 (28.4)	36 (5.7)	11 (1.7)	<0.001*	<0.001*	0.001*	<0.001*

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Table 1. Continued

	Whole Population (N=2791)	HFrEF (n=1539)	HFmrEF (n=623)	HFpEF (n=629)	$P_{HFrEF\ vs\ HFmrEF}$	$P_{HFrEF\ vs\ HFpEF}$	$P_{HFmrEF\ vs\ HFpEF}$	*P* Value
CRT-P	279 (10.0)	282 (18.3)	59 (9.4)	7 (1.1)	<0.001*	<0.001*	<0.001*	<0.001*
CRT-D	703 (25.2)	723 (47.0)	67 (10.7)	4 (0.7)	<0.001*	<0.001*	<0.001*	<0.001*
Echocardiographic findings								
LVEF, %	38.3±12.6	28.9±6.5	44.4±3.4	55.9±6.5	<0.001*	<0.001*	<0.001*	<0.001*
LVEDVi, mL/m^2	84.0±39.9	107.0±33.4	47.6±41.2	40.0±26.2	<0.001*	<0.001*	<0.001*	<0.001*
LVESVi, mL/m^2	61.9±26.7	76.3±27.3	43.7±13.1	51.0±17.7	<0.001*	<0.001*	<0.001*	<0.001*
Posterior wall thickness, mm	10.2±1.9	9.9±1.8	10.33±1.95	10.74±1.91	<0.001*	<0.001*	<0.001*	<0.001*
Septal thickness, mm	11.3±2.7	10.7±2.3	11.75±2.85	12.28±2.98	<0.001*	<0.001*	0.001*	<0.001*
LVMI, mg/m^2	135±38	146.8±37.4	126.76±33.44	116.42±35.65	<0.001*	<0.001*	<0.001*	<0.001*
LA diameter, mm	45.6±7.0	46.8±6.8	44.3±6.8	43.9±7.1	<0.001*	<0.001*	0.860	<0.001*
E/A	1.27±0.90	1.41±1.01	1.09±0.70	1.14±0.75	<0.001*	<0.001*	1.000	<0.001*
Deceleration time, ms	197±65	184±65	206.94±61.97	213.65±61.68	<0.001*	<0.001*	0.338	<0.001*
RV diameter, mm	28.2±5.2	28.5±5.8	27.42±3.91	28.07±4.70	<0.001*	0.234	0.093	<0.001*
Systolic PAP, mm Hg	39.6±12.6	41.5±12.9	36.36±12.30	38.13±11.28	<0.001*	<0.001*	0.101	<0.001*
TAPSE, mm	18.4±5.1	17.3±5.0	19.11±4.92	20.05±4.94	<0.001*	<0.001*	0.014*	<0.001*

Data are shown as n (%), mean±SD, or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, β-blockers; CKD, chronic kidney disease (eGFR ≤60 mL/min per 1.73 m^2); COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; hs, high-sensitivity; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LA, left atrium; LBBB, left-bundle branch block; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end-systolic volume; LVMI, indexed left ventricular mass; MRA, mineralocorticoid antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PRA, plasma renin activity; RBBB, right bundle-branch block; RV, right ventricle; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.

*Statistically significant.

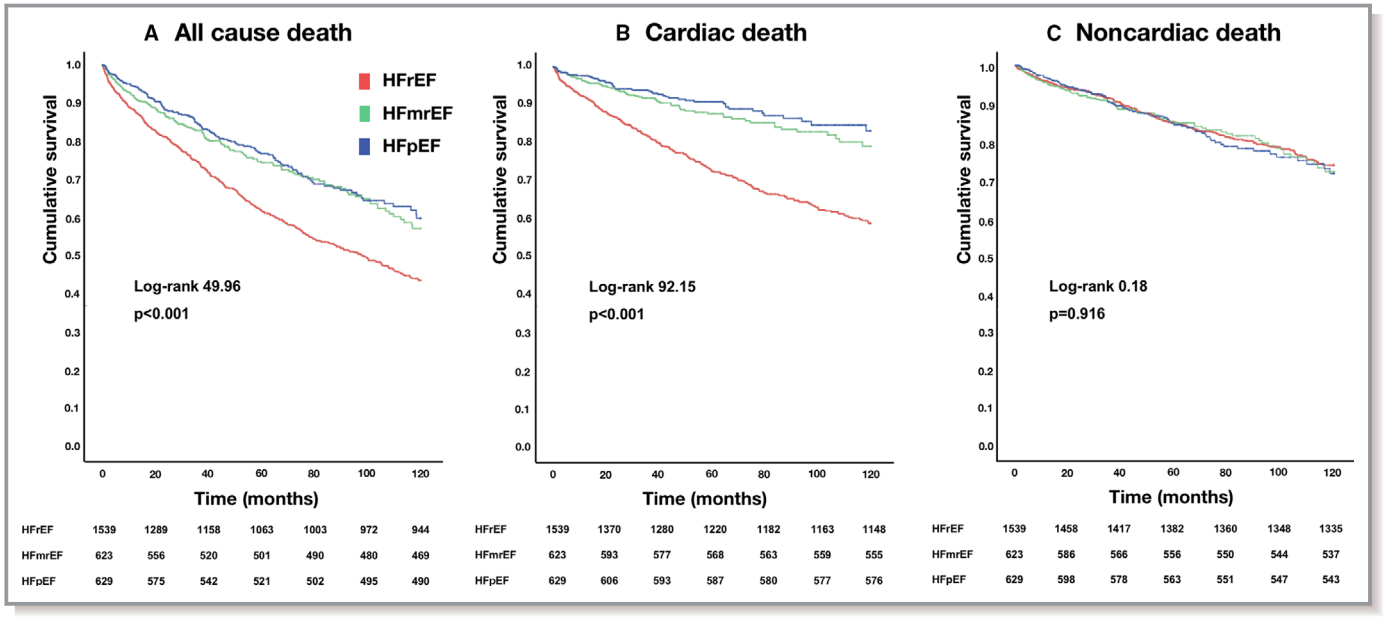

Figure 1. Mortality in patients with HFrEF, HFmrEF, and HFpEF. Kaplan-Meier curves are shown for all-cause (**A**), cardiac (**B**), and noncardiac (**C**) mortality in patients with HFrEF, HFmrEF, and HFpEF. HFmrEF indicates heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

for multiple pairwise comparisons, as appropriate. Two-tailed $P<0.05$ was considered significant. Survival was assessed with Kaplan–Meier analysis; differences in survival between groups were tested with the log-rank test (Mantel-Cox). Cardiac death and noncardiac death were considered competing outcomes.

Multivariable Cox proportional hazards models were used to estimate the adjusted hazard of HFpEF and HFmrEF

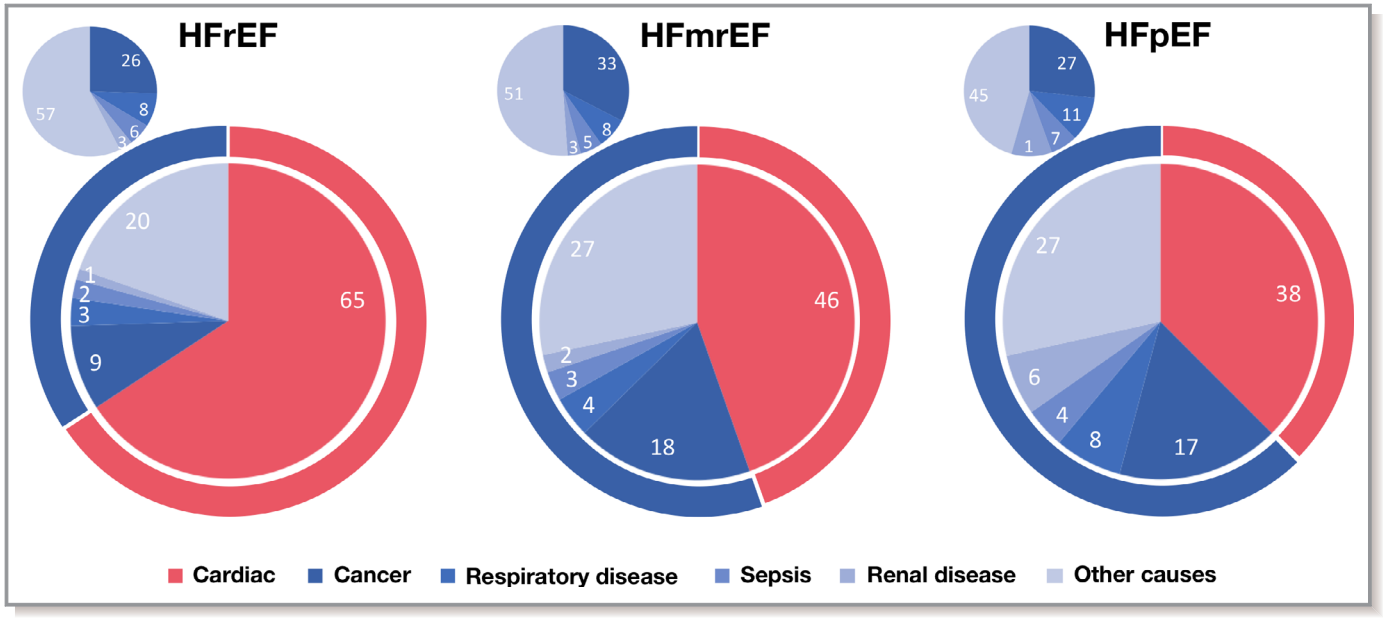

Figure 2. Prevalence of cardiac and noncardiac causes of death in patients with HFrEF, HFmrEF, and HFpEF. Prevalence of noncardiac and cardiac causes among all deaths are presented in large pies charts. Prevalence of each single cause among noncardiac deaths only is shown in small pie charts. Noncardiac causes of death were, as a whole, similarly prevalent in patients with HFmrEF and HFpEF (54% and 62%, respectively; $P=0.400$), whereas they were less frequent in HFrEF (35%; $P<0.001$ vs HFpEF and HFmrEF). Cancer was the single most prevalent noncardiac cause of death across the whole spectrum of systolic function. HFmrEF indicates heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

compared with HFrEF for time to all-cause, cardiac, and noncardiac death. Covariates were selected a priori based on clinical relevance for this HF cohort and included age, sex, etiology (ischemic versus nonischemic), New York Heart Association (NYHA) functional class, and log(NT-proBNP). In addition, Cox proportional regression analysis was used to identify predictors of cardiac and noncardiac death in each LVEF subgroup (HFrEF, HFmrEF, and HFpEF). Univariate analysis was performed for variables with known or potential influence on patient outcome: age, sex, ischemic etiology, NYHA class, hemoglobin, estimated glomerular filtration rate, log(NT-proBNP), left bundle-branch block, LVEF, tricuspid annular plane systolic excursion, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid antagonists, diuretics, cardiac resynchronization therapy, implantable cardioverter-defibrillator); univariate predictors were pooled into multivariable models to identify independent predictors.

Results

Patient Characteristics

We prospectively enrolled 2791 patients who were classified according to LVEF as having HFrEF (n=1539, 55%), HFmrEF (n=623, 22%), or HFpEF (n=629, 23%).

The baseline demographic and clinical characteristics of the whole population and of subgroups with HFrEF, HFmrEF, and HFpEF are summarized in Table 1.

Patients with HFpEF were older and more often female and had lower hemoglobin values compared with those with HFmrEF and HFrEF; furthermore, hypertension was more frequent, whereas ischemic etiology was less prevalent in HFpEF (all $P<0.05$). Patients with HFrEF had lower systolic blood pressure and more severe symptoms. Patients with HFmrEF presented on the whole with intermediate characteristics between HFrEF and HFpEF. Regarding neurohormones, patients with HFrEF displayed a higher degree of activation compared with HFmrEF and HFpEF, the 2 latter presenting with similar profiles. As expected, patients with HFpEF were less frequently treated with drugs for neurohormonal antagonism, and the use of devices was largely reserved to patients with HFrEF (Table 1).

Patients with HFrEF presented with larger LV and left atrial volumes, worse right ventricular systolic function (as estimated by tricuspid annular plane systolic excursion), and higher LV mass (all $P<0.001$), whereas HFpEF patients had greater septal and posterior wall thickness (both $P<0.001$). Concerning echocardiographic findings, patients with HFmrEF showed intermediate characteristics between HFmrEF and HFpEF (Table 1).

All-Cause Mortality in HFrEF, HFmrEF, and HFpEF

Median follow-up duration was 39 months for the whole population (IQR: 17–79 months), 40 months for HFrEF (IQR: 16–81 months), 38 months for HFmrEF (IQR: 19–82 months), and 40 months for HFpEF (IQR: 20–75 months). Information about causes of death was obtained from death certificates in 678 (72%) cases, from family doctors in 207 (22%) cases, and from postmortem reports in 56 (6%) cases.

During follow-up, 34% of the patients died; the highest crude mortality was observed with HFrEF (n=631, 41%), followed by HFmrEF (n=166, 27%) and HFpEF (n=144, 23%; log-rank: 49.19; $P<0.001$). The same trend was confirmed at 10-year Kaplan–Meier analysis. The 1-year all-cause mortality rate was 11% for HFrEF, 8% for HFmrEF, and 5% for HFpEF (log-rank: 19.94; $P<0.001$). Five-year rates were 31% for HFrEF, 20% for HFmrEF, and 17% for HFpEF (log-rank: 45.61;

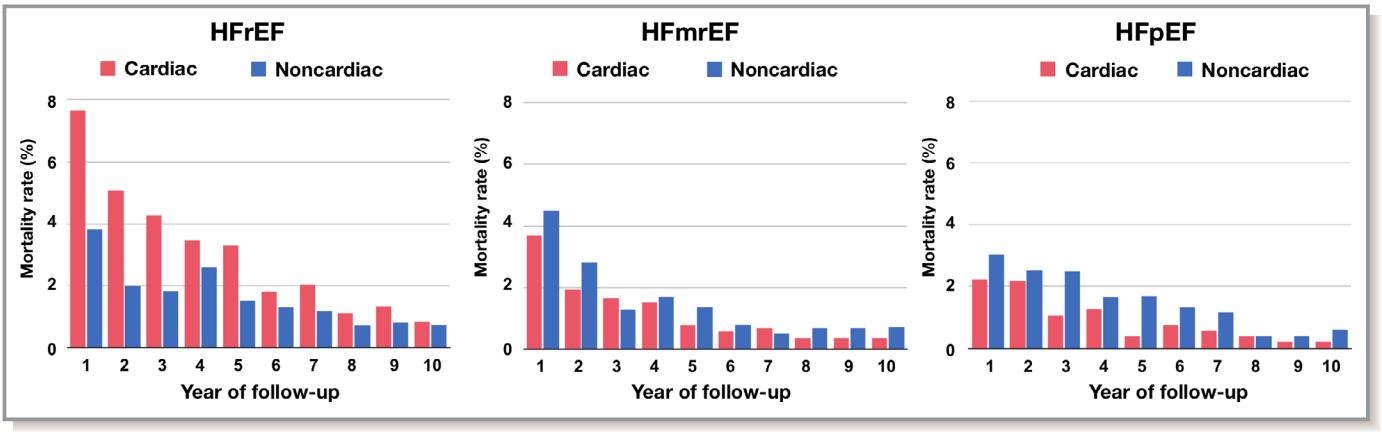

Figure 3. Yearly rates of cardiac and noncardiac death in patients with HFrEF, HFmrEF, and HFpEF. Mortality rates for either cardiac and noncardiac death in each year after enrollment are reported separately for each ejection fraction class. HFmrEF indicates heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

$P<0.001$). Finally, 10-year all-cause mortality was 39% for HFrEF, 25% for HFmrEF, and 22% for HFpEF (log-rank: 49.96; $P<0.001$; Figure 1A).

In a Cox proportional hazards model including age, sex, etiology, NYHA class, and log (NT-proBNP), patients with HFpEF and HFmrEF had lower mortality than those with HFrEF (hazard ratio [HR]: 0.75 [95% CI, 0.67–0.84], $P<0.001$ for HFpEF; HR: 0.78 [95% CI, 0.63–0.96], $P=0.017$ for HFmrEF).

Causes of Death in HFrEF, HFmrEF, and HFpEF

Considering cardiac death, patients with HFrEF again showed the poorest outcome, with 1-year cardiac mortality of 8% compared with 4% and 2% for HFmrEF and HFpEF, respectively (log-rank: 26.16; $P<0.001$). Similarly, cardiac mortality was higher in HFrEF than in HFmrEF and HFpEF at both 5-year follow-up (21% versus 9% versus 7%, respectively; log-rank: 67.60; $P<0.001$) and 10-year follow-up (25% versus 11% versus 8%, respectively; log-rank: 80.26; $P<0.001$; Figure 1B). Conversely, noncardiac mortality rates in HFrEF, HFmrEF, and HFpEF were similar at each time point (3%, 4%, and 3% at 1-year follow-up; 10%, 11%, and 10% at 5-year follow-up; 14%, 14%, and 14% at 10-year follow-up, respectively; Figure 1C).

Cardiac mortality was prevalent in HFrEF (n=415, 65% of all deaths); HF progression, sudden cardiac death, acute myocardial infarction, other cardiac causes of death, and heart transplantation were reported in 277 (44% of all deaths), 59 (9%), 27 (4%), 24 (4%), and 28 (4%) patients, respectively. Cancer, respiratory diseases, sepsis, and renal disease accounted for 55 (9%), 18 (3%), 12 (2%), and 7 (1%) deaths, respectively. Less than half of patients with HFmrEF (n=74, 46%) died from cardiac causes (HF progression: n=40, 24% of all deaths; sudden cardiac death: n=11, 7%; acute myocardial infarction: n=10, 7%; other cardiac causes of death: n=11, 7%; heart transplantation: n=2, 1%), whereas 30 (18%), 7 (4%), 5 (3%), and 3 (2%) died because of cancer, respiratory diseases, sepsis, and renal disease, respectively. Finally, HFpEF patients showed the lowest proportion of cardiac death (n=54, 38%; $P=0.400$ versus HFmrEF, $P<0.001$ versus HFrEF; HF progression: n=37, 26% of all deaths; sudden cardiac death: n=6, 4%; acute myocardial infarction: n=7, 5%; other cardiac causes of death: n=4, 3%; heart transplantation: n=0, 0%). In HFpEF, comorbidities accounted for 62% of deaths (cancer: n=24, 17%; respiratory disease: n=10, 7%; sepsis: n=6, 4%; renal disease: n=9, 6%; Figure 2). The relative distribution of cardiac and noncardiac deaths along the whole spectrum of LVEF is shown in Figure S1.

As shown in Figure 3, yearly rates of noncardiac death exceeded those of cardiac death from the beginning of follow-up in patients with HFpEF and HFmrEF. Conversely, in HFrEF, rates of cardiac death were consistently higher than noncardiac death throughout the whole follow-up period.

Predictors of Cardiac and Noncardiac Mortality

Predictors of cardiac and noncardiac death are presented in Tables 2 through 4. At multivariable analysis, independent predictors of cardiac death in HFrEF were NT-proBNP (HR: 1.60 [95% CI, 1.25–2.05]; $P<0.001$), LVEF (HR: 0.94 [95% CI, 0.90–0.97]; $P=0.011$), and absence of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (HR: 0.31 [95% CI, 0.17–0.55]; $P<0.001$); predictors in HFmrEF were age (HR: 1.06 [95% CI, 1.00–1.11]; $P=0.048$) and hemoglobin (HR: 0.76 [95% CI, 0.59–0.99]; $P=0.038$);

Table 2. Multivariate Predictors of Cardiac and Noncardiac Death in Patients With HFrEF

	B	Hazard Ratio	95% CI	*P* Value
Cardiac death				
Age	0.030	1.030	0.999–1.062	0.061
Ischemic etiology	0.211	1.235	0.783–1.947	0.364
NYHA class III/IV	0.022	1.022	0.602–1.735	0.935
Hemoglobin	0.068	1.071	0.943–1.216	0.293
eGFR	−0.002	0.998	0.987–1.009	0.733
BB	−0.592	0.553	0.272–1.125	0.102
ACEI/ARB	−1.170	0.310	0.174–0.552	<0.001*
Diuretics	0.619	1.857	0.752–4.586	0.179
NT-proBNP	0.470	1.601	1.250–2.049	<0.001*
LBBB	−0.386	0.680	0.380–1.218	0.195
LVEF	−0.061	0.941	0.897–0.986	0.011*
LVESVi	0.001	1.000	0.989–1.011	0.957
TAPSE	−0.012	0.988	0.936–1.043	0.660
Noncardiac death				
Age	0.045	1.046	1.026–1.067	<0.001*
Ischemic etiology	0.271	1.312	0.981–1.755	0.067
NYHA class III/IV	0.234	1.264	0.939–1.700	0.122
Hemoglobin	−0.157	0.855	0.784–0.932	<0.001*
eGFR	−0.007	0.993	0.986–1.000	0.066
BB	−0.620	0.538	0.364–0.796	0.002*
ACEI/ARB	−0.290	0.748	0.512–1.094	0.135
Diuretics	0.330	1.390	0.792–2.442	0.252

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end-systolic volume; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
*Statistically significant.

Table 3. Multivariate Predictors of Cardiac and Noncardiac Death in Patients With HFmrEF

	B	Hazard Ratio	95% CI	*P* Value
Cardiac death				
Age	0.053	1.055	1.001–1.112	0.048*
NYHA class III/IV	0.035	1.036	0.414–2.593	0.940
Hemoglobin	−0.271	0.762	0.590–0.985	0.038*
eGFR	−0.008	0.992	0.973–1.011	0.403
ACEI/ARB	−0.489	0.614	0.243–1.550	0.301
Diuretics	−0.430	0.650	0.208–2.034	0.460
NT-proBNP	0.270	1.310	0.943–1.820	0.107
TAPSE	−0.041	0.960	0.888–1.038	0.306
Noncardiac death				
Age	0.021	1.021	0.988–1.056	0.208
NYHA class III/IV	0.441	1.555	0.882–2.741	0.127
Hemoglobin	−0.163	0.850	0.728–0.992	0.039*
eGFR	−0.012	0.988	0.976–1.001	0.060
BB	−0.553	0.587	0.318–1.082	0.088
ACEI/ARB	−0.503	0.605	0.339–1.078	0.088
Diuretics	0.289	1.335	0.676–2.637	0.405
NT-proBNP	−0.003	0.997	0.836–1.189	0.970

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with midrange ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
*Statistically significant.

predictors in HFpEF were NT-proBNP (HR: 1.65 [95% CI, 1.19–2.28]; *P*=0.003) and diuretic use (HR: 9.09 [95% CI, 1.17–70.31]; *P*=0.035). Independent predictors of noncardiac death in HFrEF were age (HR: 1.05 [95% CI, 1.03–1.07]; *P*<0.001), hemoglobin (HR: 0.86 [95% CI, 0.78–0.93]; *P*<0.001), and absence of β-blockers (HR: 0.54 [95% CI, 0.36–0.80]; *P*=0.002); the predictor in HFmrEF was hemoglobin (HR: 0.85 [95% CI, 0.73–0.99]; *P*=0.039); predictors in HFpEF were age (HR: 1.05 [95% CI, 1.00–1.10]; *P*=0.049) and estimated glomerular filtration rate (HR: 0.98 [95% CI, 0.96–0.99]; *P*=0.006).

NT-proBNP and Outcome

To test the association of plasma level of NT-proBNP with patient outcome in each LVEF category, we plotted the HRs for cardiac and noncardiac death by each quartile of NT-proBNP, adjusted for age, sex, and estimated glomerular filtration rate. Although the risk of cardiac death increased for each increase in NT-proBNP quartile in HFrEF, HFmrEF, and HFpEF, the HRs for noncardiac death were roughly similar from the second to the fourth NT-proBNP quartile, independent of LVEF class (Figure 4).

Discussion

Comorbidities and Outcomes in HF

With this study we provide a detailed report on the different impact of main noncardiac comorbidities on mortality in patients with stable HF, with or without impairment of LVEF. During a long-term follow-up, cancer, sepsis, and respiratory and renal diseases accounted together for 15%, 27%, and 35% of deaths in patients with HFrEF, HFmrEF and HFpEF, respectively, demonstrating greater influence of noncardiac conditions on prognosis in patients with no or mild LV systolic dysfunction.

Although we report a higher prevalence of noncardiac causes among decedents in HFmrEF and HFpEF (even higher than previously reported from randomized clinical trials and epidemiological studies),[17] the crude rates of noncardiac death were similar across LVEF categories at all time points. The excess in all-cause mortality reported in patients with HFrEF is thus following a larger amount of deaths due to cardiac causes (particularly early after the beginning of follow-

Table 4. Multivariate Predictors of Cardiac and Noncardiac Death in Patients With HFpEF

	B	Hazard Ratio	95% CI	*P* Value
Cardiac death				
Age	0.004	1.004	0.961–1.049	0.868
NYHA class III/IV	0.364	1.440	0.622–3.332	0.395
Hemoglobin	0.131	1.140	0.909–1.430	0.257
eGFR	−0.009	0.991	0.974–1.009	0.314
Diuretics	2.207	9.087	1.174–70.313	0.035*
MRA	−0.264	0.768	0.336–1.757	0.532
NT-proBNP	0.498	1.646	1.186–2.284	0.003*
TAPSE	−0.085	0.919	0.830–1.017	0.103
Noncardiac death				
Age	0.048	1.049	1.000–1.101	0.049*
NYHA class III/IV	−0.068	0.934	0.447–1.954	0.857
Hemoglobin	−0.183	0.833	0.679–1.022	0.080
eGFR	−0.021	0.979	0.964–0.994	0.006*
BB	0.094	1.099	0.489–2.472	0.819
ACEI/ARB	−0.704	0.495	0.242–1.010	0.053
NT-proBNP	0.009	1.009	0.771–1.322	0.945
LVESVi	0.002	1.002	0.984–1.020	0.837

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; LVESVi, indexed left ventricular end-systolic volume; MRA, mineralocorticoid antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.
*Statistically significant.

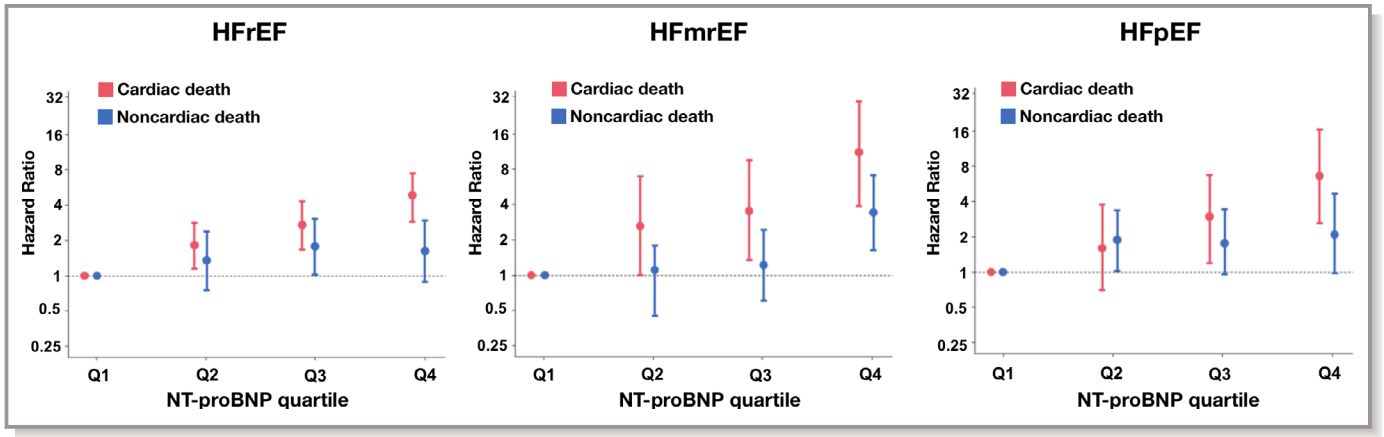

Figure 4. NT-proBNP and outcome in patients with HFrEF, HFmrEF, and HFpEF. Adjusted hazard ratios for cardiac and noncardiac death by each quartile of NT-proBNP in patients with HFrEF, HFmrEF, and HFpEF. Hazard ratios were adjusted for age, sex, and estimated glomerular filtration rate. The lowest quartile for each category of heart failure was used as reference. NT-proBNP values in each quartile were as follows: HFrEF (ng/L): Q1, <770; Q2, 770 to 1811; Q3, 1812 to 4736; Q4, >4736; HFmrEF (ng/L): Q1, <301; Q2 301 to 799; Q3, 800 to 2266; Q4, >2266; HFpEF (ng/L): Q1, <283; Q2 283 to 657; Q3, 658 to 1834; Q4, >1834. HFmrEF indicates heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

up). This result suggests that HF has a minor prognostic impact in HFmrEF and HFpEF patients, in whom comorbidities (particularly cancer) predominate as determinants of outcome well before cardiac condition. Cancer is recognized as a major cause of mortality in HFpEF, accounting for more than a third of deaths in prospective registries.[25] In addition, it has been reported to have a major influence on mortality in patients with either LVEF <50% or ≥50% in an analysis of the Swedish Heart Failure Registry.[26]

Prevalence of chronic kidney disease in patients with HFmrEF and HFpEF (32% for both categories) was intermediate compared with reports from large international registries.[13,27] Interestingly, although chronic kidney disease was less common in our cohort and estimated glomerular filtration rate was higher in subgroups with HFmrEF and HFpEF compared with HFrEF, participants displayed a higher crude rate of deaths due to renal disease (2% and 6% versus 1%, respectively). Therefore, during our long-term follow-up, even mildly deteriorated renal function may have overcome cardiac-related mortality as a prognostic determinant in some patients without major impairment of LV systolic function. Similarly, chronic obstructive pulmonary disease was equally prevalent across LVEF categories, but respiratory causes accounted for a significant amount of deaths (8%) in HFpEF only and were less frequent in HFrEF (3%) and in HFmrEF (4%), suggesting that worsening pulmonary function leads to fatal outcomes before cardiac mortality occurs in a significant subset of patients with HFpEF. Notably, both chronic kidney disease and chronic obstructive pulmonary disease were among the noncardiac comorbidities most contributing to adverse outcomes in a community-based cohort of HFpEF and HFrEF.[28]

Outcome of HFmrEF

Data from large registries have described HFmrEF as an intermediate phenotype between HFrEF and HFpEF regarding many of the most relevant clinical characteristics.[11,29] We also observe that HFmrEF has intermediate all-cause and cardiac mortality rates (although much closer to those of HFpEF) at 1-, 5-, and 10-year follow-up. Furthermore, we provide a detailed report of the mode of death of patients with HFmrEF. Although all-cause and cardiovascular mortality rates have been described previously for patients with HFmrEF,[12,29] there are limited data on noncardiac causes of death. Interestingly, we observed that although the proportions of deaths due to renal, respiratory, and infectious diseases were similar for HFrEF and HFmrEF, cancer was responsible for death in HFmrEF twice as frequently as in HFrEF (18% versus 9%). Such an observation is consistent with our finding that noncardiac deaths are predominant in HFmrEF and, even more, in HFpEF, suggesting that HF has a less severe phenotype and a lower impact on patient outcome compared with patients with HFrEF.

Predictors of Cardiac Versus Noncardiac Death

At multivariable analysis, NT-proBNP showed independent predictive value for cardiac death in patients with HFrEF and HFpEF. Although lower LV systolic function and lack of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were both expectedly associated with cardiac mortality in HFrEF, diuretic use predicted cardiac mortality in HFpEF, possibly reflecting more severe diastolic

dysfunction and disease stage. Alternatively, such findings may be explained by an unloading overtreatment in patients whose signs and symptoms of HF involve several mechanisms, including renal and pulmonary comorbidities, thus possibly precipitating hypotension and worsening hemodynamics.

In our cohort, noncardiac mortality was consistently predicted by variables directly or indirectly associated with extracardiac conditions, namely advanced age, renal function, anemia, and pulmonary disorders (as likely reflected by the lack of β-blocker therapy).

NT-proBNP and Cardiac Versus Noncardiac Mortality in HFrEF, HFmrEF, and HFpEF

Several studies have consistently demonstrated that NT-proBNP is a powerful prognostic tool in patients with HFrEF.[30] Although fewer data are available for stable patients with HFmrEF and HFpEF, the results of some large clinical trials such as PEP-CHF (The Perindopril in Elderly People with Chronic Heart Failure) and I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) support a role for NT-proBNP in risk stratification in these subsets.[31,32] A prospective longitudinal study from New Zealand and Singapore previously showed that the risk of all-cause death is similar at a given level of NT-proBNP regardless of EF class.[14] With the current study, we have further investigated the issue of prognostic relevance of NT-proBNP across LVEF, distinguishing between cardiac and noncardiac death. Indeed, NT-proBNP proved to be associated with cardiac death and was much less predictive of noncardiac death in a similar fashion in HFrEF, HFmrEF, and HFpEF. Such results suggest that although elevation of NT-proBNP can be found because of common noncardiac comorbidities,[33] it remains a predictor of disease-specific outcome in patients with HF, independent of LV systolic function.

Study Limitations

We enrolled patients from a single tertiary center in Italy; therefore, our results may not be extended to other populations with different ethnicity and/or from other geographical areas. Furthermore, because we performed a single baseline evaluation, we could not identify patients with recovered EF, whose outcomes may be different from other HF categories.[34]

Conclusions

Noncardiac causes of death have major prognostic relevance for patients with stable chronic HF, particularly subgroups with preserved or mildly impaired LVEF. Common comorbidities, such as cancer, sepsis, and respiratory or renal diseases, are crucial determinants of outcome, especially in patients with HFmrEF and HFpEF, who may present with a less severe disease-specific phenotype and thus warrant dedicated and enhanced therapeutic effort.

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Disclosures

None.

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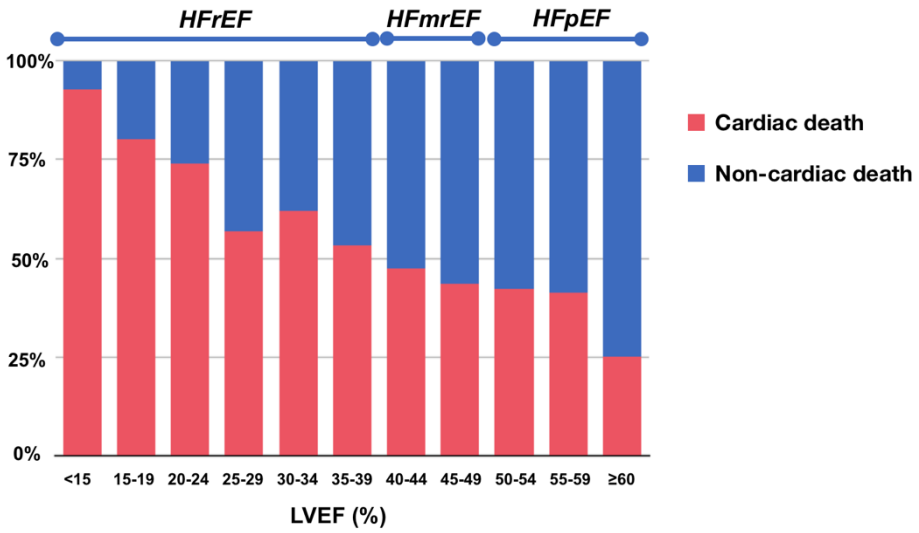
SUPPLEMENTAL MATERIAL

Figure S1. Relative distribution of cardiac and non-cardiac deaths across the whole spectrum of left ventricular ejection fraction



LVEF, left ventricular ejection fraction.