Title: Epidemiology and long-term outcome in outpatients with chronic heart failure in north-western Europe

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Abstract

Objective: To describe the epidemiology, long-term outcomes and temporal trends in mortality in ambulatory patients with chronic heart failure (HF) with reduced (HFrEF), mid-range (HFmrEF) or preserved ejection fraction (HFpEF) from three European countries.

Methods: We identified 10,312 patients from the Norwegian HF Registry and the HF registries of the universities of Heidelberg, Germany, and Hull, UK. Patients were classified according to baseline left ventricular ejection fraction (LVEF) and time of enrolment (period 1: 1995-2005 vs. period 2: 2006-2015). Predictors of mortality were analysed by use of univariable and multivariable Cox regression analyses.

Results: Among 10,312 patients with stable HF, 7,080 (68.7%), 2,086 (20.2%), and 1,146 (11.1%) were classified as having HFrEF, HFmrEF, or HFpEF, respectively. A total of 4,617 (44.8%) patients was included in period 1, and 5,695 (55.2%) patients were included in period 2. Baseline characteristics significantly differed with respect to type of HF and time of enrolment. During a median follow-up of 66 (33-105) months, 5,297 patients (51.4%) died. In multivariable analyses, survival was independent of LVEF category ($p>0.05$), while mortality was lower in period 2 as compared to period 1 (HR 0.81, 95% CI 0.72-0.91, $p<0.001$). Significant predictors of all-cause mortality regardless of HF category were increasing age, NYHA functional class, NT-proBNP, and use of loop diuretics.

Conclusion: Ambulatory HF patients stratified by LVEF represent different phenotypes. However, after adjusting for a wide range of covariates, long-term survival is independent of LVEF category. Outcome significantly improved during the last two decades irrespective from type of HF.

Words: 250

Key questions

What is already known about this subject?

Heart failure (HF) is a major cause of morbidity and mortality in Europe. Patients who suffer from HF with reduced ejection fraction (HFrEF) differ from those with preserved ejection fraction (HFpEF) with respect to demographical characteristics, comorbidities and response to therapies. Little is known about the epidemiology and characteristics of patients with HF with mid-range ejection fraction (HFmrEF).

What does this study add?

The present study describes the epidemiology, long-term outcomes and temporal trends in mortality in ambulatory patients with chronic HFrEF, HFmrEF or HFpEF from three European countries.

How might this impact on clinical practice?

Patients with HFmrEF have distinct demographical and clinical characteristics. Although crude mortality is lower compared to patients with HFrEF, outcome is independent from HF category at a given NT-proBNP level. Therefore, measurement of NT-proBNP is crucial for risk stratification of HF patients.

Introduction

According to heart failure (HF) guidelines, HF may be classified with respect to left ventricular ejection fraction (LVEF) into HF with reduced (HFrEF) or preserved ejection fraction (HFpEF) [1]. While HFrEF has been generally defined as LVEF <40%, LVEF thresholds for the definition of HFpEF have varied in clinical trials from >40% to >50%, leaving the LVEF range of 40-50% as a "grey area". The 2016 European Society of Cardiology (ESC) HF guidelines have recently defined HF with mid-range LVEF (HFmrEF) to accommodate such patients [1]. Patients with HFrEF differ from those with HFpEF: they tend to be younger, are more likely to be male, to have ischaemic HF and to respond to therapies targeted at neurohormonal activation; whereas patients with HFpEF are older, more likely to be women, to be in atrial fibrillation and to have antecedent hypertension. Little is known about the epidemiology and characteristics of patients with HFmrEF [2, 3, 4, 5].

Pharmacological and device therapies have substantially improved survival in patients with HFrEF over recent decades [1, 6, 7, 8], whereas no specific treatment has yet been shown to reduce mortality in patients with HFmrEF or HFpEF [1, 2]. As patients with HFmrEF have frequently been excluded from randomised trials, prospective outcome data in this patient population are scarce [2].

The ESC HF Long-Term (ESC-HF-LT) Registry has recently reported data on clinical characteristics and outcomes of ≈9,000 patients with HF (2,212 patients with HFmrEF) [3]. This register, however, does not include patients from Norway, the United Kingdom (UK) or Germany, and outcome data are restricted to 12 months follow-up. In the present manuscript, we present characteristics of 11,028 HF patients from HF registers in Norway, UK, and Germany, extended to long-term outcome, and with respect to HF category and period of enrolment.

Methods

Databases

Patient data were extracted from three European HF registries:

The Norwegian HF Registry was initiated in October 2000 and patients were enrolled from the outpatient clinics of 27 recruiting hospitals well distributed in all regions of Norway, ranging in size and scope from small community to large university hospitals. Patient data were registered at first contact with the patient (visit 1), after individual optimization of HF treatment (visit 2), and again 6 months after visit 2 (visit 3). The participating centres recorded their data using a web-based database, and mortality data were obtained at regular intervals from the National Statistics Bureau, Statistics Norway. For the purpose of the present manuscript, patient data registered at the last available visit were analysed.

Patients who attended the community HF clinics of the University of Heidelberg, Germany, and the University of Hull, UK, for evaluation of HF were offered inclusion into the local HF registries. The HF registries were initiated in December 1995 and March 2001, respectively. Since both university hospitals are providers of secondary and tertiary care, the registries reflect a broad representation of patients of their respective regions. Patients were included after stabilization of both clinical status and medication. Determination of survival status and follow-up were performed by scheduled visits to the outpatient clinics, by telephone calls either to the patients' homes or to their physicians, or by electronic hospital records. For the purpose of the present analysis, patients were censored as "alive" at the date of this last contact. All surviving patients were followed for ≥6 months. All-cause mortality was the primary endpoint of the present study.

Recruitment was prospective and continuous for each database and centre [9]. All patients gave their written informed consent for data storage and evaluation. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees.

The diagnosis of HF was established according to guidelines on the basis of typical symptoms and signs consistent with the diagnosis associated with an objective abnormality of cardiac structure or function on echocardiography, cardiac magnetic resonance imaging, or left heart catheterisation. In patients with normal or mildly reduced LVEF, evidence of a relevant structural heart disease (e.g. left ventricular hypertrophy or left atrial enlargement) and/or diastolic dysfunction was required. Baseline characteristics included medical history, physical examination, LVEF, blood chemistry, and medication. Medication was at the discretion of the referring physician. Glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula [10].

Statistical analysis

Patient data were stratified according to their LVEF and time of enrolment into the HF registry. In order to examine changes in therapy and outcome over time, we divided the patients into two cohorts: those recruited between 1995 and 2005 (period 1); and those recruited between 2006 and 2015 (period 2). 2005 was used as a cut-off for three reasons: 1. to give two similar sized populations, 2. to compare outcomes between two decades, 3. new HF guidelines were introduced in 2005. HFrEF, HFmrEF, and HFpEF were defined according to the 2016 ESC HF guidelines as LVEF <40%, 40-49%, and ≥50%, respectively [1].

All tests are two-tailed and a *P*-value of less than 5% was regarded as being statistically significant. Variables are presented as mean±standard deviation, median (interquartile range), or number (percentages (%)) as appropriate. Chi-squared tests were used to compare categorical variables. To test for significant differences between two groups, the Man-Whitney-U test or Student's t-test were used. To test for significant differences between three or more groups, the Kruskal-Wallis test or analyses of variance (ANOVA) tests were used where appropriate. Differences in survival with respect to class of HF and/or time period were analysed using Cox proportional hazard models and displayed using the Kaplan-Meier method.

All variables that were statistically significant in univariable analyses by LVEF group or time period were included in multivariable Cox regression models with backwards elimination to identify predictors for all-cause mortality. A significance level of 5% was required to allow a variable both to be entered into and to stay in the multivariable models. Statistics were calculated using MedCalc® version 18.11.3 (MedCalc Software bvba, Ostend, Belgium).

Results

Characteristics

From December 1995 to November 2015, a total of 11,028 ambulatory patients with stable chronic HF was enrolled into the three registries. Of these, 7,080 patients (64.2%) were classified as having HFrEF, 2,086 patients (18.9%) as having HFmrEF, and 1,146 patients (10.4%) as having HFpEF. In 716 (6.5%) patients, no information on LVEF was available. They were therefore excluded from further analyses. The distribution of HF categories in the three registries is shown in *supplemental table 1*.

Baseline characteristics and treatment significantly differed between patients with HFrEF, HFmrEF, or HFpEF, respectively (*Tables 1-2*).

Table 1: Baseline characteristics of HF patients with respect to type of HF

	All patients (n = 10,312)	**HFrEF (n = 7,080)**	**HFmrEF (n = 2,086)**	**HFpEF (n = 1,146)**	**p-value**
Age, *years*	66.7 ± 13.4	66.6 ± 12.6	67.3 ± 14.1	65.9 ± 16.8	*0.02*
Female, *n (%)*	2,738 (26.6)	1,674 (23.6)	610 (29.2)	454 (39.6)	*<0.001*
BMI, *kg/m²*	27.2 ± 5.3	26.9 ± 5.2	27.9 ± 5.5	27.0 ± 5.3	*<0.001*
SBP, *mmHg*	125 ± 22	123 ± 22	129 ± 23	128 ± 22	*<0.001*
HR, *1/min*	70 ± 14	71 ± 14	69 ± 14	69 ± 13	*<0.001*
Sinus rhythm, *n (%)*	6,405 (67.7)	4,429 (68.1)	1,287 (66.4)	689 (67.5)	0.39
LVEF, *%*	34 ± 12	27 ± 7	43 ± 3	57 ± 7	*<0.001*
Cause of HF, *n (%)*					*<0.001*
ischaemic	5,161 (53.8)	3,781 (58.1)	1,067 (53.9)	313 (28.6)	
non-ischaemic	4,424 (46.2)	2,731 (41.9)	911 (46.1)	782 (71.4)	
NYHA class, *n (%)*					*<0.001*
I/II	6,767 (66.5)	4,504 (64.5)	1,470 (71.8)	783 (69.5)	
III/IV	3,403 (33.5)	2,481 (35.5)	579 (28.1)	343 (30.5)	
Comorbidity, *n (%)*					
Diabetes mellitus	2,128 (20.6)	1,458 (20.7)	456 (21.9)	214 (18.7)	0.11
Hypertension	4,209 (40.8)	2,595	967 (46.4)	647 (56.7)	*<0.001*

		(36.8)			
COPD/ asthma	1,232 (11.9)	885 (12.6)	229 (11.0)	118 (10.3)	*0.03*
Smoker, *n (%)**	3,430 (37.3)	2,285 (36.5)	788 (41.3)	357 (34.7)	*<0.001*
Sodium, *mmol/L*	139 ± 4	139 ± 4	140 ± 3	140 ± 3	0.11
Potassium, *mmol/L*	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	*<0.001*
NTproBNP, *pg/mL*	1,008 (305-2,605)	1,301 (482-3,169)	652 (180-1,759)	316 (100-1,302)	*<0.001*
eGFR, *ml/min/1.73m²*	67 (49-86)	66 (49-84)	68 (50-88)	71 (50-92)	*<0.001*
Time of enrolment, *n (%)*					*<0.001*
Period 1	4,617 (44.8)	3,325 (47.0)	850 (40.7)	442 (38.6)	
Period 2	5,695 (55.2)	3,755 (53.0)	1,236 (59.3)	704 (61.4)	

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; period 1: 1995-2005, period 2: 2006-2015. *former or active smokers. Significant p-values are written in italics.

Table 2: Treatment of HF patients with respect to type of HF

Treatment	**All patients (n = 10,312)**	**HFrEF (n = 7,080)**	**HFmrEF (n = 2,086)**	**HFpEF (n = 1,146)**	**p-value**
ACEI, *n (%)*	7,219 (70.0)	5,131 (72.6)	1,430 (68.7)	658 (57.5)	*<0.001*
Captopril	174 (2.4)	138 (2.7)	21 (1.5)	15 (2.3)	*0.03*
Enalapril	1,135 (15.7)	836 (16.3)	178 (12.4)	121 (18.4)	*<0.001*
Lisinopril	906 (12.6)	637 (12.4)	197 (13.8)	72 (10.9)	0.17
Ramipril	4,794 (66.4)	3,377 (65.8)	985 (68.9)	432 (65.7)	0.09
Trandolapril	12 (0.2)	8 (0.2)	4 (0.3)	0 (0.0)	0.33
Other	197 (2.7)	134 (2.6)	45 (3.1)	18 (2.7)	0.55
ARB, *n (%)*	1,915 (18.6)	1,304 (18.5)	376 (18.1)	235 (20.6)	0.36
ACEI and/or ARB, *n (%)*	8,867 (86.0)	6,231 (88.5)	1,763 (84.9)	873 (76.4)	*<0.001*
ACEI/ARB dose equivalent, *%*	50 (25-100)	75 (50-100)	50 (50-100)	50 (50-100)	*<0.001*
Beta-blocker, *n (%)*	8,482 (82.3)	5,992 (84.8)	1,662 (79.8)	828 (72.5)	*<0.001*
Bisoprolol	1,425 (16.8)	943 (15.7)	320 (19.3)	162 (19.6)	*<0.001*
Carvedilol	2,275 (26.8)	1,728 (28.8)	391 (23.5)	156 (18.8)	*<0.001*
Metoprolol succinate	4,208 (49.6)	2,989 (49.9)	783 (47.1)	436 (52.7)	*0.03*
Nebivolol	160 (1.8)	83 (1.4)	42 (2.5)	35 (4.2)	*<0.001*
Other	414 (4.9)	249 (4.2)	126 (7.6)	39 (4.7)	*<0.001*
Beta-blocker dose equivalent, *%*	50 (13-75)	50 (25-100)	50 (25-75)	50 (25-75)	0.10
MRA, *n (%)*	3,098 (30.0)	2,360 (33.4)	508 (24.4)	230 (20.1)	*<0.001*
Loop diuretics, *n (%)*	7,288 (70.7)	5,387 (76.1)	1,266 (60.7)	635 (55.4)	*<0,001*
Loop diuretic dose,	40 (0-80)	40 (40-80)	40 (40-80)	40 (40-80)	0.36

mg furosemide					
Anticoagulants, *n (%)*	4,492 (43.6)	3,271 (46.3)	790 (37.9)	431 (37.7)	*<0.001*
ASA, *n (%)*	4,411 (42.8)	3,063 (43.3)	936 (44.9)	412 (36.0)	*<0.001*
Statin, *n (%)*	5,784 (56.1)	4,038 (57.1)	1,209 (58.0)	537 (46.9)	*<0.001*

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, Acetylsalicyl acid. Significant p-values are written in italics.

A total of 4,617 patients (44.8%) was included into the HF registries in period 1, whereas 5,695 patients (55.2%) were enrolled in period 2. Baseline characteristics and treatment of patients with respect to time periods are shown in *Tables 3 -4*. Baseline characteristics with respect to HF category and time of enrolment are presented in *Supplemental tables 2-4*.

Table 3: Baseline characteristics of HF patients with respect to time of enrolment into the heart failure registries (period 1: 1995-2005, period 2: 2006-2015)

	All patients (n = 10,312)	**Period 1 (n = 4,617)**	**Period 2 (n = 5,695)**	**p-value**
Age, *years*	66.7 ± 13.4	68.1 ± 12.5	65.5 ± 14.0	*<0.001*
Female, *n (%)*	2,738 (26.6)	1,213 (27.4)	1,525 (26.8)	0.56
BMI, *kg/m²*	27.2 ± 5.3	26.9 ± 5.2	27.4 ± 5.4	*<0.001*
SBP, *mmHg*	125 ± 22	126 ± 23	124 ± 21	*<0.001*
HR, *1/min*	70 ± 14	71 ± 15	70 ± 14	*<0.001*
Sinus rhythm, *n (%)*	6,405 (67.7)	2,719 (68.5)	3,686 (64.7)	*<0.001*
LVEF, *%*	34 ± 12	33 ± 12	34 ± 12	*<0.001*
Type of HF, *n (%)*				
HFrEF	7,080 (70.7)	3,325 (72.0)	3,755 (65.9)	*<0.001*
HFmrEF	2,086 (18.9)	850 (18.4)	1,236 (21.7)	*<0.001*
HFpEF	1,146 (10.4)	442 (9.6)	704 (12.4)	*<0.001*
Cause of HF, *n (%)*				*<0.001*
ischaemic	5,161 (53.8)	2,533 (60.1)	2,628 (48.9)	
non-ischaemic	4,424 (46.2)	1,682 (39.9)	2,742 (51.1)	
NYHA class, *n (%)*				*<0.001*
I	2,014 (19.8)	666 (14.7)	1,348 (24.0)	
II	4,753 (46.7)	2,255 (49.6)	2,498 (44.4)	
III	3,273 (32.2)	1,564 (34.4)	1,709 (30.4)	
IV	130 (1.3)	59 (1.3)	71 (1.3)	
Comorbidity, *n (%)*				
Diabetes mellitus	2,128 (20.6)	835 (18.1)	1,293 (22.7)	*<0.001*
Hypertension	4,209 (40.8)	1,338 (29.0)	2,871 (50.4)	*<0.001*
COPD/ asthma	1,232 (11.9)	503 (10.9)	729 (12.8)	*0.003*
Smoker, *n (%)*				*<0.001*

ever	3,430 (37.3)	1,702 (40.2)	1,728 (34.6)	
never	5,763 (62.7)	2,534 (59.2)	3,229 (65.4)	
Sodium, *mmol/L*	139 ± 4	139 ± 4	140 ± 4	0.24
Potassium, *mmol/L*	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	*<0.001*
NTproBNP, *ng/L*	1,008 (305-2,605)	1,046 (399-2,635)	991 (278-2,595)	*0.01*
eGFR, *ml/min/1.73m²*	67 (49-86)	62 (46-81)	71 (52-90)	*<0.001*
HF registry, *n (%)*				*<0.001*
Norway	6,122 (59.4)	2,936 (63.6)	3,186 (55.9)	
Heidelberg	2,368 (23.0)	710 (15.4)	1,658 (29.1)	
Hull	1,822 (17.7)	971 (21.0)	851 (14.9)	

HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; . Significant p-values are written in italics.

Table 4: Treatment of HF patients with respect to time of enrolment into the heart failure registries (period 1: 1995-2005, period 2: 2006-2015)

	All patients (n = 10,312)	**Period 1 (n = 4,617)**	**Period 2 (n = 5,695)**	**p-value**
ACEI, *n (%)*	7,219 (70.0)	3,302 (71.5)	3,917 (68.8)	*0.003*
Captopril	174 (2.4)	144 (4.4)	30 (0.8)	*<0.001*
Enalapril	1,135 (15.7)	679 (20.6)	456 (11.6)	*<0.001*
Lisinopril	906 (12.6)	600 (18.2)	306 (7.8)	*<0.001*
Ramipril	4,794 (66.4)	1,753 (53.1)	3,041 (77.6)	*<0.001*
Trandolapril	12 (0.2)	10 (0.3)	2 (0.0)	*0.009*
Other	197 (2.7)	116 (3.5)	81 (1.4)	*<0.001*
ARB, *n (%)*	1,915 (18.6)	643 (13.9)	1,272 (22.3)	*<0.001*
ACEI and/or ARB, *n (%)*	8,867 (86.0)	3,865 (83.7)	5,002 (87.8)	*<0.001*
ACEI/ARB dose equivalent, *%*	50 (25-100)	50 (25-100)	50 (25-100)	0.07
Beta-blocker, *n (%)*	8,482 (82.3)	3,486 (75.5)	4,996 (87.7)	*<0.001*
Bisoprolol	1,425 (16.8)	348 (10.0)	1,077 (21.6)	*<0.001*
Carvedilol	2,275 (26.8)	1,096 (31.4)	1,179 (23.6)	*<0.001*
Metoprolol succinate	4,208 (49.6)	1,719 (49.3)	2,489 (49.8)	0.64
Nebivolol	160 (1.8)	30 (0.9)	130 (2.3)	*<0.001*
Other	414 (4.9)	293 (8.4)	121 (2.1)	*<0.001*
Beta-blocker dose equivalent, *%*	50 (13-75)	25 (4-75)	50 (25-79)	*<0.001*
MRA, *n (%)*	3,098 (30.0)	1,247 (27.0)	1,851 (32.5)	*<0.001*
Loop diuretics, *n (%)*	7,288 (70.7)	3,555 (77.0)	3,733 (65.5)	*<0,001*
Loop diuretic dose, *mg furosemide*	40 (0-80)	40 (20-80)	40 (0-80)	*<0,001*

Anticoagulants, *n (%)*	4,492 (43.6)	2,102 (45.5)	2,390 (42.0)	*<0.001*
ASA, *n (%)*	4,411 (42.8)	1,783 (38.6)	2,628 (46.1)	*<0.001*
Statin, *n (%)*	5,784 (56.1)	2,260 (48.9)	3,524 (61.9)	*<0.001*

HF, heart failure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, Acetylsalicyl acid. Significant p-values are written in italics.

Outcome

Of 10,312 patients included in the three HF registries, 5,297 (51.4%) died during a median follow-up of 66 (33-105) months. Of these, 3,836 patients (72.4%) were classified as having HFrEF, 957 (18.1%) as having HFmrEF, and 504 (9.5%) as having HFpEF. Kaplan-Meier curves for 10-year survival with respect to type of HF are shown in *Figure 1*.

Of 4,617 patients enrolled in period 1, 3,204 (69.4%) died during a median follow-up of 66 (32-106) months. Of 5,695 patients enrolled in period 2, 2,093 (36.8%) died during a median follow-up of 66 (33-105) months. Kaplan-Meier curves for 10-year survival with respect to time of enrolment are shown in *Figure 2*. As presented in *Supplemental figure 1*, survival of HF outpatients gradually increased since 1995. *Supplemental figure 2* shows Kaplan-Meier curves for 10-year survival with respect to type of HF and time of enrolment.

1-, 2-, 3-, 4-, and 5-year mortality rates for HF patients with respect to LVEF and time of enrolment are presented in *Table 5*.

Table 5: All-cause mortality rates of HF patients with respect to LVEF group and time of enrolment.

All-cause death	All patients (n=10,312)	Period 1 (n=4,617)	Period 2 (n=5,695)	HFrEF			HFmrEF			HFpEF		
				All patients (n=7,080)	Period 1 (n=3,325)	Period 2 (n=3,755)	All patients (n=2,086)	Period 1 (n=850)	Period 2 (n=1,236)	All patients (n=1,146)	Period 1 (n=442)	Period 2 (n=704)
1-year	6.1	8.1	4.5	6.8	8.5	5.4	4.1	5.5	3.2	5.4	9.7	2.7
2-years	13.3	16.8	10.6	14.4	17.6	11.5	10.7	12.9	9.1	11.9	17.9	8.2
3-years	20.0	24.3	16.5	21.2	25.1	17.7	17.5	20.9	15.1	17.4	25.1	12.5
4-years	25.9	31.5	21.4	27.5	32.2	23.2	22.7	27.5	19.4	22.4	33.5	15.5
5-years	31.4	38.2	25.9	33.2	39.0	28.1	27.2	33.3	23.1	27.6	41.2	19.0

HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; n, number. Figures given represent percentages.

In univariable Cox regression analyses of the general sample, a diagnosis of HFmrEF or HFpEF was associated with better survival as compared to HFrEF (HR 0.84, 95%-CI 0.78-0.90, p<0.001 for HFmrEF vs. HFrEF, and HR 0.90, 95%-CI 0.82-0.99, p=0.03 for HFpEF vs. HFrEF). Survival was similar in patients with HFmrEF or HFpEF (HR 1.08, 95%-CI 0.97-1.20, p=0.15). Survival significantly improved between time periods (HR 0.74, 95%-CI 0.69-0.78, p<0.001). This was true irrespective of the HF category (HR 0.76, 95%-CI 0.71-0.81, p<0.001 for HFrEF, HR 0.80, 95%-CI 0.70-0.91, p=0.001 for HFmrEF, and HR 0.55, 95%-CI 0.45-0.66, p<0.001 for HFpEF).

In multivariable regression analyses of the general sample including all variables that were significant in univariable analyses (data not shown), survival was independent of type of HF (p=0.34 for HFmrEF vs. HFrEF and p=0.84 for HFpEF vs. HFrEF). However, this was only true when NT-proBNP was included in the model. In contrast, survival was better in period 2 as compared to period 1 irrespective from NT-proBNP concentrations (HR 0.85, 95%-CI 0.76-0.95, p=0.004). Complete results of multivariable regression analyses are shown in *Table 6*.

Table 6: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HF (general sample).

Variable	**HR**	**95% CI**	**p-value**
Age, *years*	1.04	1.03-1.04	*<0.0001*
NYHA class, *vs. NYHA class I*			
II	1.23	1.04-1.46	*0.02*
III	1.74	1.46-2.07	*<0.0001*
IV	1.90	1.26-2.87	*0.002*
Aetiology, *non-ischaemic vs. ischaemic*	0.82	0.74-0.91	*0.0002*
Diabetes mellitus, *yes vs. no*	1.19	1.06-1.33	*0.003*
COPD/ asthma, *yes vs. no*	1.28	1.11-1.47	*0.0007*
Hypertension, *yes vs. no*	1.18	1.07-1.31	*0.001*
logNTproBNP	2.00	1.80-2.22	*<0.0001*
eGFR, *ml/min/1.73m²*	0.996	0.993-0.998	*0.002*
Sodium, *mmol/l*	0.97	0.96-0.99	*0.0002*
MRA, *yes vs. no*	1.18	1.06-1.32	*0.004*
Loop diuretic, *yes vs. no*	1.44	1.26-1.65	*<0.0001*
Time of enrolment, *period 2 vs. period 1*	0.85	0.76-0.95	*0.004*

HF, heart failure; HR, hazard ratio; CI, confidence interval; HR, heart rate; NYHA, New York Heart Association functional class; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; MRA, mineralocorticoid receptor antagonist. Non-significant covariates were body mass index, sex, heart rate, sinus rhythm (yes vs. no), smoker (ever vs. never), potassium level, use of angiotensin converting enzyme inhibitors/ angiotensin receptor blockers, use of beta blockers, use of statins, use of aspirin, use of anticoagulants, left ventricular ejection fraction category.

Significant predictors of all-cause mortality differed between HF categories. Results from multivariable analyses in subgroups of patients with HFrEF, HFmrEF or HFpEF are depicted

in *Supplemental Tables 5-7*. *Supplemental Tables 8-9* show results from multivariable analyses in subgroups with respect to time to enrolment.

Discussion

Chronic HF is a major cause of serious morbidity and mortality in Europe [1, 7, 8]. In the present manuscript, we present a comprehensive dataset including baseline characteristics and long-term follow-up of ambulatory patients with chronic HF from three different European countries.

We found that patients stratified by categories of LVEF and/or time of enrolment differ with respect to baseline variables including demography, clinical presentation, cause of HF, co-morbidities and medical treatment. However, long-term survival was independent of HF category, whereas it was significantly better in patients enrolled in period 2 as compared to period 1.

The majority of patients presented with HFrEF, while only few patients were classified as having HFpEF. Although the number of patients with a diagnosis of HFpEF increased over time, HFpEF was less frequent as compared to data from community-based studies. However, the proportion of HFpEF was similar to that reported from the ESC-HF-LT Registry – suggesting that HFpEF patients rarely present at specialized HF outpatient clinics [3, 11]. 18.9% of patients had HFmrEF, which is similar to other estimates of the prevalence of HFmrEF in the overall HF population [2].

As with previous studies, patients with HFrEF were predominantly male and more likely to suffer from symptomatic HF of ischaemic origin than patients presenting with HFpEF [2, 3, 5, 11, 12, 13, 14, 15, 16, 17, 18]. This was true for the entire study duration. Our data also confirm the high prevalence of hypertension in the HFpEF population. Clinical characteristics of HFmrEF were intermediate between those of HFrEF and HFpEF for some important variables including sex distribution, comorbidities, NT-proBNP levels and renal function.

However, the proportion of ischaemic HF in HFmrEF was comparable to that in HFrEF, suggesting that HFmrEF may represent early-stage or recovered HFrEF [2, 3, 5, 12]. Similar results have been reported from clinical trial and registry cohorts [2, 3, 5, 15].

In contrast to a number of previous studies describing higher age of patients with HFpEF [2, 3, 5, 11, 12, 13, 14, 15, 16, 17, 18], we found no clinically significant differences in mean age between HF categories. However, patients with HFpEF enrolled in period 2 were ten years younger as compared to those enrolled in period 1. In addition, sinus rhythm was more common in period 2, and NT-proBNP concentrations were significantly lower. Thus, patients with a diagnosis of HFpEF differed substantially between periods, and it may be questioned whether the diagnosis “HFpEF” was correct in all cases. The majority of patients with HFrEF received guideline-recommended treatment with ACEIs/ARBs and beta-blockers, and one third additionally used MRAs. Although there is a lack of evidence for their use in HFmrEF and HFpEF, these medications were also used in a substantial proportion of patients with LVEF >40%. A similar finding has been reported from the ESC-HF-LT Registry as well as from a recently published prospective longitudinal study [3, 5]. The proportion of patients taking ACEIs/ARBs and beta-blockers increased irrespective of HF category over time. When comparing the proportion of patients with guideline-recommended medical HFrEF treatment in the present study to other Western European HF cohorts of the respective time periods, a similar [3, 5, 15, 19, 20] or higher [13, 14, 21, 22, 23, 24] rate of adequate HFrEF treatment can be noted. This may be explained by the enrolment of stable HF patients in specialized HF outpatient clinics (in contrast to primary care settings).

All-cause mortality of the complete patient sample was 6.1% after one year and increased to 31.4% after five years. One-year mortality was similar to that observed in other European HF registries (5.9-8.1%) but lower when compared to a Spanish cohort study of ambulatory HF patients (10%) [3, 27, 28]. Five-year mortality was substantially lower when compared to the Danish National Patient Registry [29], retrospective data from Sweden [30] or a recent analysis of the Get With The Guidelines-HF (GWTG-HF) registry (43-75.4%) [4]. Of note, all

of these studies included patients with acute HF and thus refer to populations that differ from the present study.

Mortality rates significantly decreased over time irrespective from the type of HF. A similar trend has been reported from the Danish National Patient Registry with a decline in one- to five-year-mortality from 59% during 1983-1987 to 43% during 2008-2013 [29]. In addition, HF age-standardized death rates have significantly decreased in seven European countries from 1987 to 2008 [6].

Crude mortality rates were higher in HFrEF as compared to HFmrEF and HFpEF. Thus, although patients with HFmrEF have many features more typical of HFrEF, their outcome resembles those of the HFpEF group more closely than those of the HFrEF group. A similar finding has been reported from the ESC-HF-LT Registry [3] and the CHARM trial [16]. After adjustment for significant covariates, however, survival of HF patients was independent from HF category. This finding is supported by several studies including the GWTG-HF registry [4, 5, 11, 14, 18]. In contrast, a meta-analysis of 31 studies [17] reported a lower risk for death within one year in patients with HFpEF as compared to those with HFrEF. Of note, the meta-analysis did only adjust for a selected number of covariates including gender, age, ischaemic aetiology, hypertension, diabetes and atrial fibrillation. In a recently published study including HF patients from New Zealand and Singapore, it was demonstrated that NT-proBNP is a major confounder of mortality in HFmrEF and HFpEF: While patients with HFmrEF or HFpEF had a lower risk of death than those with HFrEF after adjusting for age, sex, and clinical risk factors, the risk of death for any HF phenotype was similar at a given level of NT-proBNP [5]. In accordance with this observation, NT-proBNP removed the crude differences in mortality between the LVEF categories in our study. NT-proBNP measurements thus provide a critical tool for clinicians to risk stratify their HF patients and seem to be of greater importance for outcomes than LVEF.

Limitations

The study population comprised only patients seen at HF outpatient clinics and did not include hospitalized patients or patients seen in a primary care setting, which may entail selection bias. The majority of HF patients, however, are followed at outpatients clinics. Therefore, outcome data on this population are important to inform clinical decisions.

In 2016, the ESC HF guidelines have introduced elevated levels of cardiac peptides as a requirement for the diagnosis of HFmrEF or HFpEF [1]. As patients in the present manuscript were enrolled between 1995 and 2015, cardiac peptide measurements were not available in all patients, and elevated cardiac peptide levels were not required for the diagnosis of HFmrEF or HFpEF. In addition, as the assessment of LVEF was not standardized, it may have been subject to variations among different operators. Both aspects may have resulted in the misclassification of some patients. Some patients may have navigated between categories of HF during the time of the study, and we do not have data to assess these patients separately. Our study includes patients from three different registries that were initiated independently from one another. However, the consistency of patient selection is warranted by inclusion of ambulatory patients with chronic stable HF after stabilization of clinical status and optimization of medical treatment. Moreover, the large sample size and prospective inclusion of patients from three European countries over a long time period are obvious strengths of the present study.

Conclusion

Chronic ambulatory HF patients stratified by categories of LVEF differ with respect to baseline variables including demography, clinical presentation, cause of HF, co-morbidities and medical treatment. Patients with HFmrEF share many clinical features with those with HFrEF. Crude mortality rates of patients with HFmrEF, however, resemble those of the HFpEF group more closely than those of the HFrEF group. After adjusting for a wide range of

covariates including NT-proBNP, long-term survival was independent from LVEF category. Survival significantly improved during the last two decades irrespective from type of HF.

Author contributorship

Hanna Fröhlich	Study design, data acquisition, statistical analysis, data interpretation, draft of the manuscript, responsible for the overall content as a guarantor
Niklas Rosenfeld	study design, data acquisition, statistical analysis, review of the manuscript
Tobias Täger	data acquisition, statistical analysis, review of the manuscript
Kevin Goode	data acquisition, statistical analysis, review of the manuscript
Syed Kazmi	data acquisition, statistical analysis, review of the manuscript
Torstein Hole	data acquisition, statistical analysis, review of the manuscript
Hugo A. Katus	review of the manuscript
Dan Atar	review of the manuscript
John G. F. Cleland	review of the manuscript
Stefan Agewall	review of the manuscript
Andrew L. Clark	study design, data acquisition, review of the manuscript
Lutz Frankenstein	study design, data acquisition, review of the manuscript, responsible for the overall content as a guarantor

Morten Grundtvig	study design, data acquisition, review of the manuscript, supervisorship, responsible for the overall content as a guarantor

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Competing interests

None declared.

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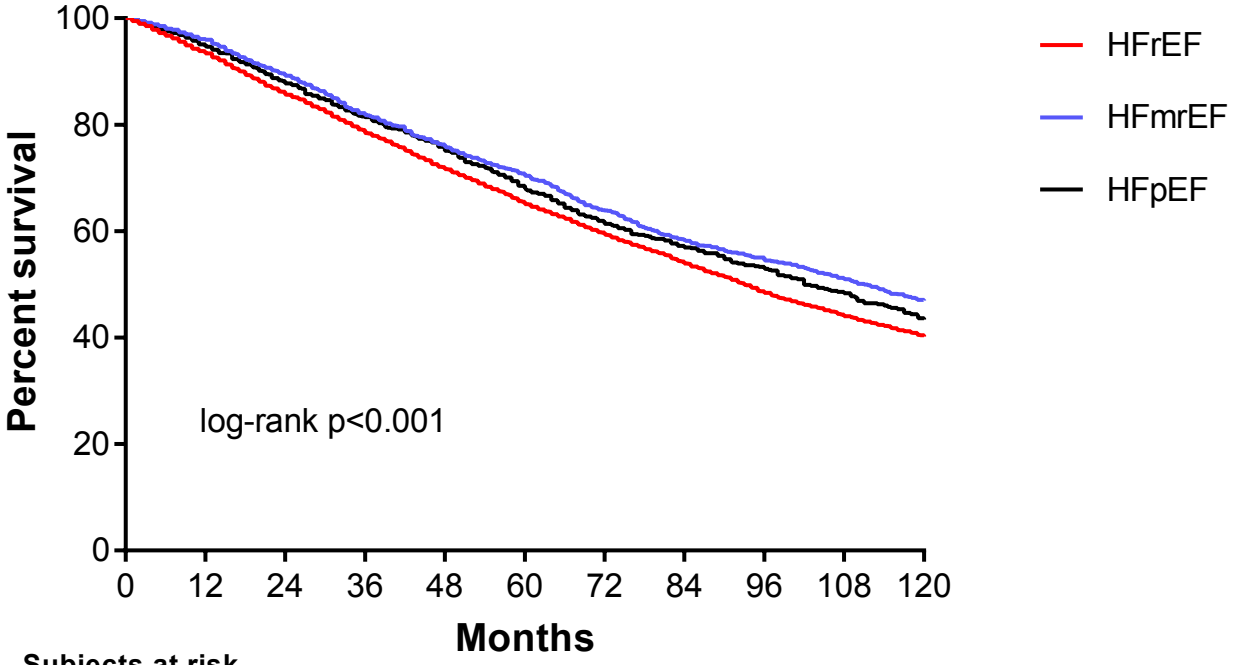
Figures

Figure 1: Kaplan-Meier curves for 10-year survival of HF outpatients with respect to type of HF.

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

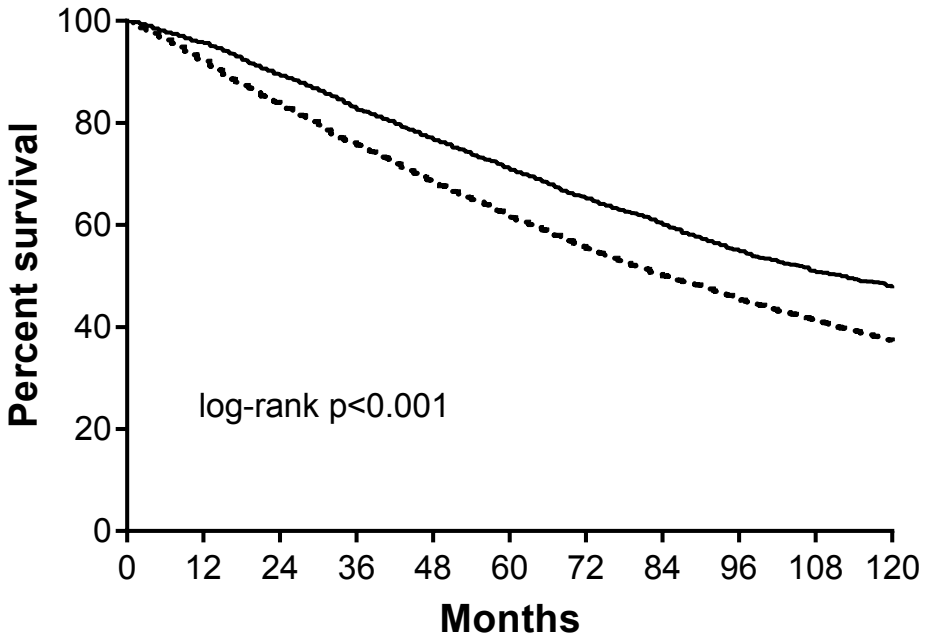
Figure 2: Kaplan-Meier curves for 10-year survival of HF outpatients with respect to time of enrollment.

HF, heart failure.



Subjects at risk

HFrEF	7 061	5 881	4 606	3 344	2 179	1 289
HFmrEF	2 084	1 780	1 371	970	640	403
HFpEF	1 114	921	667	451	313	174



Subjects at risk

1995-2005	4 606	3 838	3 111	2 497	1 951	1 516
2006-2015	5 683	4 744	3 533	2 268	1 181	350

Supplemental material

Supplemental table 1: Distribution of HF categories in the three registries

HF registry	All patients (n = 10,312)	HFrEF (n = 7,080)	HFmrEF (n = 2,086)	HFpEF (n = 1,146)	p-value
Norway	6,122 (59.4)	4,561 74.5)	998 (16.3)	563 (9.2)	*<0.001*
Heidelberg	2,368 (23.0)	1,385 (58.5)	526 (22.2)	457 (19.3)	*<0.001*
Hull	1,822 (17.7)	1,134 (62.2)	562 (30.8)	126 (6.9)	*<0.001*

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction

Supplemental table 2: Baseline characteristics of HFrEF patients with respect to time of enrolment.

	HFrEF (n = 7,080)		**p-value**
	Period 1 (n = 3,325)	**Period 2 (n = 3,755)**	
Age, *years*	67.4 ± 12.2	65.9 ± 12.9	*<0.001*
Female, *n (%)*	763 (22.9)	911 (24.3)	0.19
BMI, *kg/m²*	26.7 ± 4.9	27.2 ± 5.5	*0.001*
SBP, *mmHg*	124 ± 22	123 ± 21	*0.001*
HR, *1/min*	71 ± 15	70 ± 14	*0.01*
Sinus rhythm, *n (%)*	1,995 (69.9)	2,434 (66.6)	*0.006*
LVEF, *%*	27 ± 7	28 ± 7	*0.006*
Cause of HF, *n (%)*			*<0.001*
ischaemic	1,902 (63.3)	1,879 (53.6)	
non-ischaemic	1,105 (36.7)	1,626 (46.4)	
NYHA class, *n (%)*			*<0.001*
I	434 (13.2)	716 (19.3)	
II	1,627 (49.6)	1,727 (46.6)	
III	1,171 (35.7)	1,207 (32.6)	
IV	46 (1.4)	57 (1.4)	
Comorbidity, *n (%)*			

Diabetes mellitus	585 (17.6)	873 (23.4)	*<0.001*
Hypertension	888 (26.8)	1,707 (45.8)	*<0.001*
COPD/ asthma	366 (11.0)	519 (13.9)	*<0.001*
Smoker, *n (%)*			*<0.001*
ever	1,286 (41.7)	999 (31.5)	
never	1,795 (58.3)	2,175 (68.5)	
Sodium, *mmol/L*	139 ± 5	139 ± 4	0.16
Potassium, *mmol/L*	4.4 ± 0.5	4.4 ± 0.5	*0.03*
NTproBNP, *ng/L*	1,277 (496-3,002)	1,311 (482-3,205)	0.92
eGFR, *ml/min/1.73m²*	62 (46-81)	69 (51-87)	*<0.001*
Treatment			
ACEI, *n (%)*	2,450 (73.7)	2,681 (71.6)	0.14
Captopril	115 (4.7)	23 (0.9)	*<0.001*
Enalapril	499 (20.4)	337 (12.6)	*<0.001*
Lisinopril	421 (17.2)	216 (8.1)	*<0.001*
Ramipril	1,324 (54.0)	2,053 (76.6)	*<0.001*
Trandolapril	6 (0.2)	2 (0.0)	0.12
Other	84 (3.4)	49 (1.8)	*<0.001*
ARB, *n (%)*	456 (13.8)	848 (22.7)	*<0.001*
ACEI and/or ARB, *n*	2,842 (85.8)	3,389 (90.8)	*<0.001*

(%)			
ACEI/ARB dose equivalent, *%*	75 (50-100)	63 (50-100)	*0.04*
Beta-blocker, *n (%)*	2,573 (77.5)	3,419 (91.2)	*<0.001*
Bisoprolol	245 (9.5)	698 (20.4)	*<0.001*
Carvedilol	888 (34.5)	840 (24.6)	*<0.001*
Metoprolol succinate	1,234 (48.0)	1,755 (51.3)	*0.01*
Nebivolol	23 (0.9)	60 (1.8)	*0.007*
Other	183 (7.1)	66 (1.9)	*<0.001*
Beta-blocker dose equivalent, *%*	50 (25-100)	50 (25-100)	*<0.001*
MRA, *n (%)*	977 (29.4)	1,383 (37.0)	*<0.001*
Loop diuretics, *n (%)*	2,629 (79.1)	2,758 (73.5)	*<0.001*
Loop diuretic dose, *mg furosemide*	40 (40-80)	40 (40-80)	*<0.001*
Anticoagulants, *n (%)*	1,558 (46.9)	1,713 (45.7)	0.33
ASA, *n (%)*	1,283 (38.6)	1,780 (47.5)	*<0.001*
Statin, *n (%)*	1,663 (50.1)	2,375 (63.4)	*<0.001*
HF registry, *n (%)*			*<0.001*
Norway	2,449 (65.2)	2,112 (63.5)	

Heidelberg	833 (22.2)	552 (16.6)	
Hull	473 (12.6)	661 (19.9)	

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; period 1, 1995-2005; period 2, 2006-2015; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, Acetylsalicyl acid. Significant p-values are written in italics.

Supplemental table 3: Baseline characteristics of HFmrEF patients with respect to time of enrolment.

	HFmrEF (n = 2,086)		**p-value**
	Period 1 (n = 850)	**Period 2 (n = 1,236)**	
Age, *years*	69.2 ± 12.6	65.9 ± 14.9	*<0.001*
Female, *n (%)*	269 (31.6)	341 (27.6)	*0.04*
BMI, *kg/m²*	27.8 ± 5.7	27.9 ± 5.3	0.64
SBP, *mmHg*	132 ± 24	127 ± 22	*<0.001*
HR, *1/min*	70 ± 14	69 ± 14	0.42
Sinus rhythm, *n (%)*	512 (68.5)	775 (65.1)	0.11
LVEF, *%*	43 ± 3	43 ± 3	*0.04*
Cause of HF, *n (%)*			*<0.001*
ischaemic	483 (60.7)	584 (46.4)	
non-ischaemic	313 (39.3)	598 (53.6)	
NYHA class, *n (%)*			*<0.001*
I	162 (19.4)	374 (30.5)	
II	433 (51.9)	511 (41.7)	
III	231 (27.7)	329 (26.9)	
IV	8 (1.0)	11 (0.9)	
Comorbidity, *n (%)*			

Diabetes mellitus	172 (20.3)	284 (23.0)	0.13
Hypertension	289 (34.0)	678 (54.9)	*<0.001*
COPD/ asthma	92 (10.8)	137 (11.1)	0.84
Smoker, *n (%)*			0.75
ever	317 (40.9)	471 (41.6)	
never	459 (59.1)	662 (58.4)	
Sodium, *mmol/L*	140 ± 3	139 ± 3	0.06
Potassium, *mmol/L*	4.4 ± 0.5	4.3 ± 0.4	*0.002*
NTproBNP, *ng/L*	667 (208-1,610)	638 (175-1,839)	0.76
eGFR, *ml/min/1.73m²*	62 (46-81)	73 (53-91)	*<0.001*
Treatment			
ACEI, *n (%)*	587 (69.1)	843 (68.4)	0.71
Captopril	18 (3.1)	3 (0.4)	*<0.001*
Enalapril	100 (17.0)	78 (9.3)	*<0.001*
Lisinopril	133 (22.7)	64 (7.6)	*<0.001*
Ramipril	312 (53.2)	673 (79.8)	*<0.001*
Trandolapril	4 (0.7)	0 (0.0)	*0.02*
Other	20 (3.4)	25 (2.9)	0.64
ARB, *n (%)*	114 (13.4)	262 (21.3)	*<0.001*
ACEI and/or ARB, *n*	689 (81.1)	1,074 (87.5)	*<0.001*

(%)			
ACEI/ARB dose equivalent, *%*	50 (50-100)	50 (50-100)	0.74
Beta-blocker, *n (%)*	626 (73.6)	1,036 (84.0)	*<0.001*
Bisoprolol	77 (12.3)	243 (23.5)	*<0.001*
Carvedilol	144 (23.0)	247 (23.8)	0.70
Metoprolol succinate	311 (49.7)	472 (45.6)	0.10
Nebivolol	5 (0.8)	37 (3.6)	*<0.001*
Other	89 (14.2)	37 (3.6)	*<0.001*
Beta-blocker dose equivalent, *%*	50 (25-75)	50 (25-100)	0.36
MRA, *n (%)*	169 (19.9)	339 (27.6)	*<0.001*
Loop diuretics, *n (%)*	589 (69.3)	677 (54.8)	*<0.001*
Loop diuretic dose, *mg furosemide*	40 (40-80)	40 (40-80)	0.55
Anticoagulants, *n (%)*	323 (38.0)	467 (37.8)	0.94
ASA, *n (%)*	369 (43.4)	567 (45.9)	0.25
Statin, *n (%)*	425 (50.0)	784 (63.5)	*<0.001*
HF registry, *n (%)*			*<0.001*
Norway	497 (58.5)	501 (40.5)	

Heidelberg	95 (11.2)	431 (34.9)	
Hull	258 (30.4)	304 (24.6)	

HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; period 1, 1995-2005; period 2, 2006-2015; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, Acetylsalicyl acid. Significant p-values are written in italics.

Supplemental table 4: Baseline characteristics of HFpEF patients with respect to time of enrolment.

	HFpEF (n = 1,146)		**p-value**
	Period 1 (n = 442)	**Period 2 (n = 704)**	
Age, *years*	72.0 ± 13.1	62.0 ± 17.7	*<0.001*
Female, *n (%)*	181 (40.9)	273 (38.8)	*0.01*
BMI, *kg/m²*	26.4 ± 5.5	27.4 ± 5.2	*0.004*
SBP, *mmHg*	131 ± 23	126 ± 21	*<0.001*
HR, *1/min*	71 ± 14	68 ± 13	*<0.001*
Sinus rhythm, *n (%)*	212 (57.9)	477 (72.8)	*<0.001*
LVEF, *%*	58 ± 8	57 ± 5	*0.002*
Cause of HF, *n (%)*			*<0.001*
ischaemic	148 (35.9)	165 (24.2)	
non-ischaemic	264 (64.1)	518 (75.8)	
NYHA class, *n (%)*			*<0.001*
I	70 (16.2)	258 (37.2)	
II	195 (45.1)	260 (37.5)	
III	162 (37.5)	173 (24.9)	
IV	5 (1.2)	3 (0.4)	
Comorbidity, *n (%)*			

Diabetes mellitus	78 (17.7)	136 (19.4)	0.49
Hypertension	161 (26.6)	486 (69.2)	*<0.001*
COPD/ asthma	45 (10.2)	73 (10.4)	0.93
Smoker, *n (%)*			*<0.001*
ever	99 (26.1)	258 (39.7)	
never	280 (73.9)	392 (60.3)	
Sodium, *mmol/L*	139 ± 3	140 ± 3	0.07
Potassium, *mmol/L*	4.4 ± 0.5	4.3 ± 0.4	*<0.001*
NTproBNP, *ng/L*	467 (224-1,489)	281 (90-1,184)	*0.01*
eGFR, *ml/min/1.73m²*	59 (44-75)	81 (56-98)	*<0.001*
Treatment			
ACEI, *n (%)*	265 (59.9)	393 (55.9)	0.19
Captopril	11 (4.1)	4 (1.0)	*0.04*
Enalapril	80 (30.2)	41 (10.4)	*<0.001*
Lisinopril	46 (17.4)	26 (6.6)	*<0.001*
Ramipril	117 (44.2)	315 (80.2)	*<0.001*
Trandolapril	0 (0.0)	0 (0.0)	n.a.
Other	11 (4.1)	7 (1.8)	0.07
ARB, *n (%)*	72 (16.3)	162 (23.1)	*0.005*
ACEI and/or ARB, *n*	334 (75.6)	539 (76.9)	0.61

(%)			
ACEI/ARB dose equivalent, *%*	50 (50-100)	50 (50-100)	0.22
Beta-blocker, *n (%)*	287 (65.1)	541 (77.2)	*0.04*
Bisoprolol	26 (9.1)	136 (25.1)	*<0.001*
Carvedilol	64 (22.6)	92 (17.0)	0.06
Metoprolol succinate	174 (60.6)	262 (48.4)	*0.001*
Nebivolol	2 (0.7)	33 (6.1)	*<0.001*
Other	21 (7.3)	18 (3.3)	*0.01*
Beta-blocker dose equivalent, *%*	50 (25-75)	50 (25-75)	0.77
MRA, *n (%)*	101 (22.9)	129 (18.3)	0.06
Loop diuretics, *n (%)*	337 (76.2)	298 (42.3)	*<0.001*
Loop diuretic dose, *mg furosemide*	40 (40-80)	40 (40-80)	0.20
Anticoagulants, *n (%)*	221 (50.0)	210 (29.9)	*<0.001*
ASA, *n (%)*	131 (29.6)	281 (40.0)	*<0.001*
Statin, *n (%)*	172 (38.9)	365 (52.0)	*<0.001*
HF registry, *n (%)*			*<0.001*
Norway	327 (73.9)	236 (33.5)	

Heidelberg	63 (14.3)	394 (56.0)	
Hull	52 (11.8)	74 (10.5)	

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; period 1, 1995-2005; period 2, 2006-2015; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; NTproBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ASA, Acetylsalicyl acid. Significant p-values are written in italics.

Supplemental table 5: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HFrEF.

Variable	HR	95% CI	p-value
Age, *years*	1.04	1.04-1.05	*<0.0001*
NYHA class, *vs. NYHA class I*			
III	1.49	1.33-1.68	*<0.0001*
IV	1.71	1.12-2.59	*0.01*
Aetiology, *non-ischaemic vs. ischaemic*	0.75	0.66-0.85	*<0.0001*
Diabetes mellitus, *yes vs. no*	1.24	1.09-1.41	*0.001*
COPD/ asthma, *yes vs. no*	1.45	1.24-1.69	*<0.0001*
Hypertension, *yes vs. no*	1.13	1.01-1.27	*0.03*
logNTproBNP	1.95	1.74-2.20	*<0.0001*
Sodium, *mmol/l*	0.97	0.96-0.99	*0.001*
Loop diuretic, *yes vs. no*	1.31	1.12-1.52	*0.0007*
Anticoagulants, *yes vs. no*	1.12	1.00-1.26	*0.05*
Time of enrolment, *period 2 vs. period 1*	0.85	0.76-0.97	*0.01*

HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association functional class; COPD, chronic obstructive pulmonary disease. Significant p-values are written in italics.

Supplemental table 6: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HFmrEF.

Variable	HR	95% CI	p-value
Age, *years*	1.03	1.02-1.04	*<0.0001*
NYHA class III, *vs. NYHA class I*	1.40	1.12-1.76	*0.003*
Hypertension, *yes vs. no*	1.27	1.03-1.57	*0.03*
logNTproBNP	2.34	1.87-2. 92	*<0.0001*
Loop diuretic, *yes vs. no*	1.93	1.49-2. 52	*<0.0001*
Sodium, *mmol/L*	0.97	0.94-0.99	*0.03*

HFmrEF, heart failure with mid-range ejection fraction; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association functional class. Significant p-values are written in italics.

Supplemental table 7: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HFpEF.

Variable	**HR**	**95% CI**	**p-value**
Age, *years*	1.04	1.01-1.06	*0.002*
NYHA class, *vs. NYHA class I*			
II	1.88	1.01-3.51	*0.05*
III	3.09	1.64-5.84	*0.0005*
Potassium, *mmol/L*	1.55	1.02-2.37	*0.04*
logNT-proBNP	2. 50	1.72-3.62	*<0.0001*
Loop diuretic, *yes vs. no*	2.48	1.48-4.13	*0.0005*
Anticoagulants, *yes vs. no*	0.67	0.45-0.99	*0.05*

HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association functional class. Significant p-values are written in italics.

Supplemental table 8: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HF enrolled in period 1.

Variable	**HR**	**95% CI**	**p-value**
Age, *years*	1.05	1.04-1.06	*<0.0001*
LVEF, *%*	0.99	0.98-0.99	*0.007*
Aetiology, *non-ischaemic vs. ischaemic*	0.84	0.70-0.99	*0.05*
NYHA class III, *vs. NYHA class I*	1.21	1.02-1.45	*0.03*
Hypertension, *yes vs. no*	1.21	1.03-1.42	*0.02*
COPD/ asthma, *yes vs. no*	1.43	1.11-1.83	*0.005*
Diabetes, *yes vs. no*	1.21	1.00-1.46	*0.05*
logNTproBNP	1.83	1.57-2.15	*<0.0001*
MRA, *yes vs. no*	1.23	1.03-1.48	*0.03*
Loop diuretic, *yes vs. no*	1.42	1.16-1.74	*0.0008*

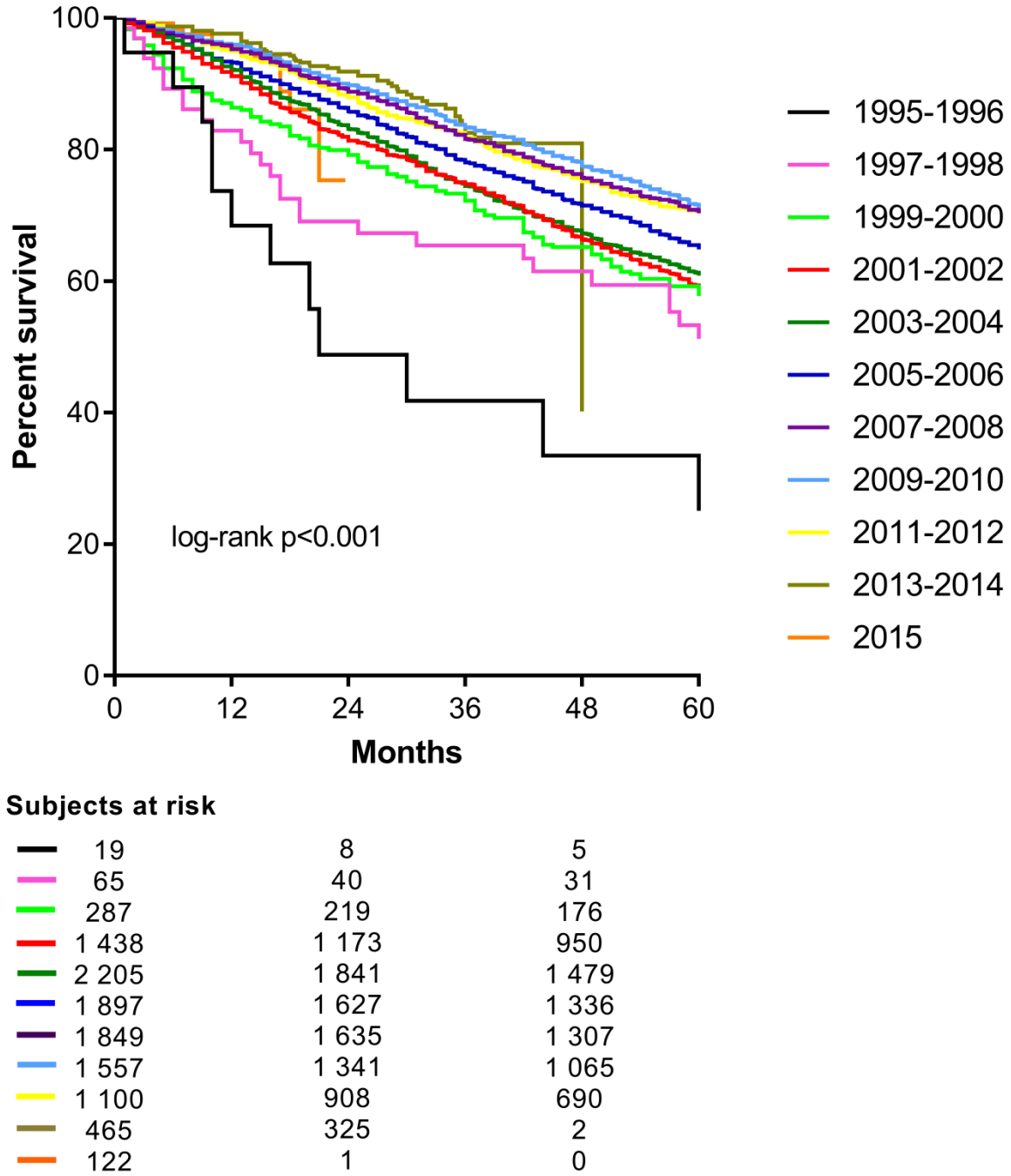
HF, heart failure; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist. Significant p-values are written in italics.

Supplemental table 9: Significant predictors of all-cause mortality in multivariable Cox regression analysis in patients with HF enrolled in period 2.

Variable	HR	95% CI	p-value
Age, *years*	1.03	1.03-1.04	*<0.0001*
Sex, *female vs. male*	0.73	0.64-0.84	*<0.0001*
BMI, *kg/m²*	0.98	0.97-0.99	*0.02*
NYHA class, *vs. NYHA class I*			
II	1.26	1.01-1.57	*0.04*
III	2.02	1.61-2.53	*<0.0001*
IV	3.40	1.98-5.83	*<0.0001*
Aetiology, *non-ischaemic vs. ischaemic*	0.85	0.75-0.97	*0.01*
Diabetes mellitus, *yes vs. no*	1.26	1.10-1.44	*0.0009*
COPD/ asthma, *yes vs. no*	1.26	1.07-1.48	*0.005*
logNTproBNP	1.96	1.72-2.24	*<0.0001*
eGFR, *ml/min/1.73m²*	0.996	0.993-0.999	*0.02*
Sodium, *mmol/l*	0.97	0.95-0.98	*0.0001*
Loop diuretic, *yes vs. no*	1.51	1.27-1.80	*<0.0001*

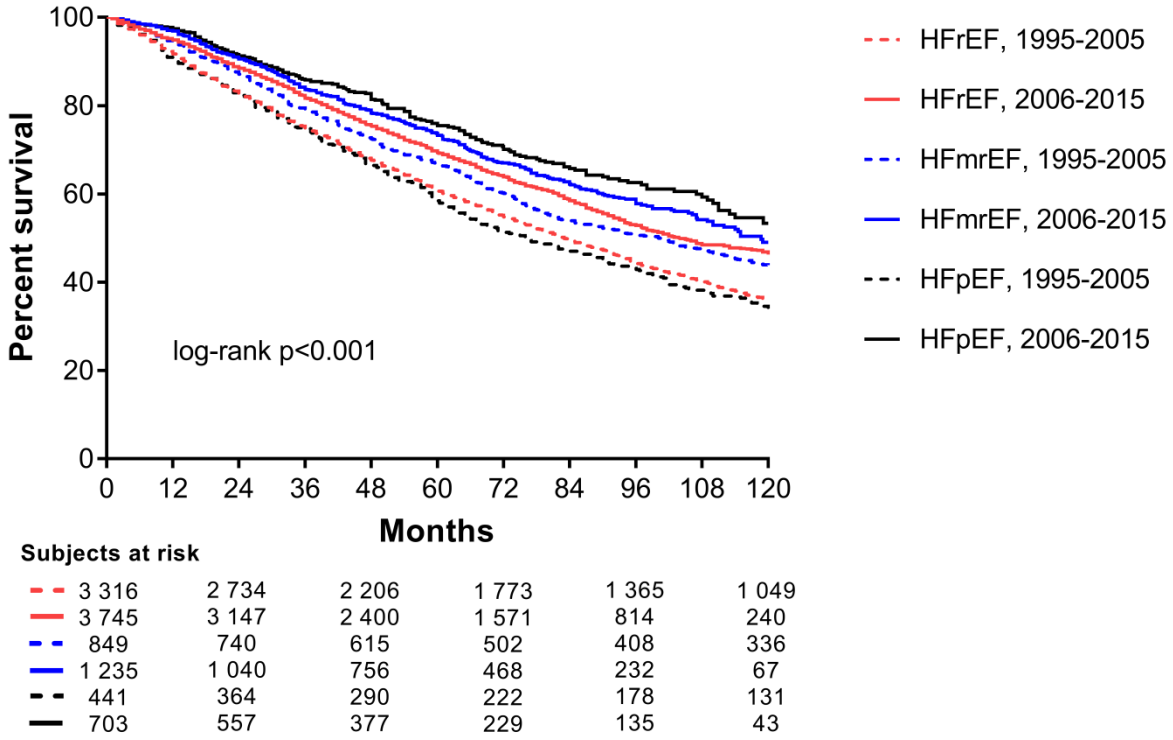
HF, heart failure; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NYHA, New York Heart Association functional class; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. Significant p-values are written in italics.

Supplemental figure 1: Kaplan-Meier curves for 5-year survival of HF outpatients stratified by two-year enrolment periods.



HF, heart failure.

Supplemental figure 2: Kaplan-Meier curves for 10-year survival of HF outpatients with respect to type of HF and time of enrolment.



Subjects at risk

HFrEF, 1995-2005	3 316	2 734	2 206	1 773	1 365	1 049
HFrEF, 2006-2015	3 745	3 147	2 400	1 571	814	240
HFmrEF, 1995-2005	849	740	615	502	408	336
HFmrEF, 2006-2015	1 235	1 040	756	468	232	67
HFpEF, 1995-2005	441	364	290	222	178	131
HFpEF, 2006-2015	703	557	377	229	135	43

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.