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## Abstract

**Background and Aims** To assess in-hospital and 1-year cause-specific outcomes in the contemporary European Society of Cardiology (ESC) Heart Failure (HF) III Registry.

**Methods** Patients were enrolled in European or ESC affiliated countries and characterized in detail regarding clinical characteristics and cause-specific outcomes.

**Results** Between 1 November 2018 and 31 December 2020, 10,162 patients were enrolled from 220 centres in 41 countries. Of these, 39% had acute HF ('AHF', age 70 [62–79] years, 36% women) and 61% had out-patient visit for HF ['out-patient HF', age 66 (58–75) years, 33% women]. Overall, 58% had HF with reduced ejection fraction (HFrEF), 17% HF with mildly

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reduced ejection fraction (HFmrEF), and 25% HF with preserved ejection fraction (HFpEF). In AHF, median [interquartile range (IQR)] duration of hospitalization was 9 (6–14) days, and 5.1% died in hospital (HFrEF 5.2%; HFmrEF 4.8%, HFpEF 3.4%). In AHF discharged alive and in out-patient HF, after a median (IQR) follow-up of 376 (360–432) days, all-cause, cardiovascular (CV), and unknown-cause mortality rates per 100 patient-years were as follows: AHF HFrEF: 19, 13, and 3.0 per 100 patient-years. The corresponding numbers were in AHF HFmrEF: 22, 11, and 6.3; AHF HFpEF: 16, 7.0, and 4.7; out-patient HFrEF: 6.6, 4.3, and 0.9; out-patient HFmrEF: 4.0, 2.6, and 0.8; out-patient HFpEF: 3.9, 1.7, and 1.2. At least one (re-)hospitalization for HF was experienced in 44% AHF HFrEF, 42% AHF HFmrEF, 36% AHF HFpEF, 21% out-patient HFrEF, 14% out-patient HFmrEF, and 18% out-patient HFpEF.

## Conclusions

In HF in Europe and affiliated countries, in-hospital mortality was 5.1% and greater with lower ejection fraction. Among hospital survivors and out-patients over 1 year of follow-up, event rates per 100 patient-years varied for death, 3.9–22, CV death 1.7–13, and unknown cause of death 0.8–6.3. The percent of patients that were (re-)hospitalized for HF at least once over 1-year follow-up ranged 14–44% and was twice as high post-AHF compared with post-out-patient visit.

## Structured Graphical abstract

### Key Question

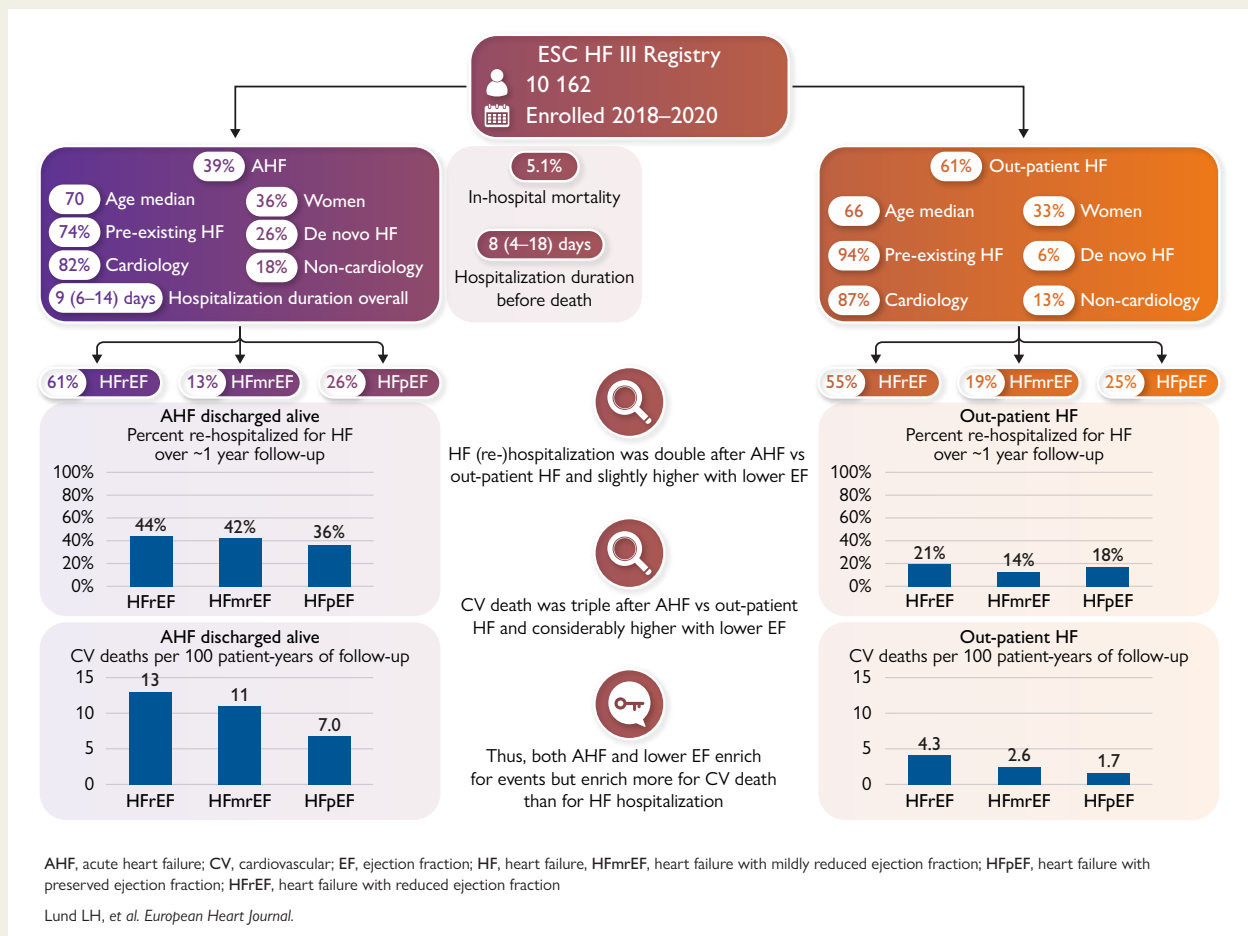
What are the outcomes of hospitalized and ambulatory patients with heart failure (HF)?

### Key Finding

In the ESC HF III Registry enrolling 10 162 patients, in-hospital mortality was 5.1%. HF (re-)hospitalization at 1 year ranged 14–44% and was double after acute HF (AHF) vs out-patient HF. Cardiovascular death rates ranged 1.7–13 per 100 patient-years.

### Take Home Message

These comprehensive outcome data provide actionable information for all stakeholders.



## Keywords

Acute heart failure • Chronic heart failure • Ejection fraction • Registry • Outcomes • Event rates • Trial design

## Introduction

Heart failure (HF) affects more than 64 million people worldwide and is increasing in prevalence, likely due to an ageing population, continuously improving treatment and survival after myocardial infarction, and improved recognition of HF with preserved ejection fraction (HFpEF).<sup>1,2</sup> HFpEF in particular is expected to increase considerably in the future.<sup>3</sup> Mortality and risk of HF hospitalization remain high and quality of life and functional capacity are poor.<sup>1,4,5</sup>

There are now extensive effective therapies for HF with reduced ejection fraction (HFrEF), suggestions that many of these may be effective in HF with mildly reduced ejection fraction (HFmrEF),<sup>3</sup> but so far only sodium-glucose co-transporter 2/1 (SGLT2/1) inhibitors and mineralocorticoid receptor antagonists appear effective across the ejection fraction (EF) spectrum.<sup>6,7</sup> In HFpEF, exercise and caloric restriction<sup>8</sup> and glucagon-like peptide-1 agonists in obesity with concurrent HFpEF<sup>9,10</sup> may be effective. Historically, patients hospitalized with acute HF (AHF) were excluded from trials of chronic HF treatment, but increasingly patients who are stable in the hospital are allowed into chronic HF trials.

There are numerous differences in characteristics and outcomes among patients with HF with different EF categories, and among patients with new-onset vs pre-existing and AHF vs out-patient HF, and in AHF, in-hospital vs post-discharge outcomes. These differences are critical to understand for clinical decision making, triage and prioritization, and for interpretation and design of clinical interventional trials. These categories have been studied individually in different registry, cohort, and trial dataset contexts, but these studies have been limited by small size, data granularity, or generalizability, and these HF categories and settings have rarely been studied together and thus there are no large generalizable granular direct comparisons between both different EF categories and in-patient vs out-patient settings. The European Society of Cardiology (ESC) HF III Registry aims to provide a large comprehensive analysis of HF in European and ESC-affiliated countries. The rationale and design,<sup>11</sup> and the first co-primary analysis from ESC HF III Registry [which provided a comprehensive analysis of baseline HF characteristics and guideline-directed medical therapy (GDMT) treatment decisions]<sup>12</sup> have been published. Here we provide the second co-primary analysis: In-hospital outcomes in AHF and 1-year outcomes in out-patient and post-AHF, and according to EF category.

## Methods

### Rationale and design

The ESC HF III Registry has been previously described.<sup>11</sup> It is a prospective, international, multicentre, observational registry study of patients with HF. It includes patients regardless of EF, with either chronic or *de novo* HF who present with a non-urgent out-patient visit or with urgent worsening HF for care in the hospitalized, emergency department, or out-patient urgent care settings, and treated with intravenous medications (diuretics, vasodilators, vasopressors, or inotropes) for HF. The objectives include providing a comprehensive data set for both discovery and implementation science. Extensive baseline data are collected. The first co-primary analysis focused on baseline use of and decision making regarding GDMT.<sup>12</sup> Here, we present the second co-primary analysis: outcomes.

### Oversight

The ESC HF III Registry is sponsored by the ESC EURObservational Research Programme (EORP; <https://www.escardio.org/Research/>

registries/eorp). The HF III Chairperson (LHL) wrote the protocol with input from the EORP Oversight Committee (Appendix 1) and from the HF III Executive Committee (Appendix 2). National coordinators (the Steering Committee, Appendix 3) coordinated national activities and liaised with the Chairman, the sponsor team at EORP, and local investigators (Appendix 4).

### Setting

The ESC HF III Registry enrolled patients with HF in European, Mediterranean and some non-European countries, affiliated with the ESC. The registry complies with the 1975 Declaration of Helsinki; the locally appointed ethics committees approved the research protocol, and informed consent was obtained from all patients. The target enrolment was 10 000 patients. Detailed data elements and time points have been described.<sup>11</sup> Data were entered manually by investigators and/or coordinators into a registry-specific electronic case report form, managed by EORP. Data were validated by EORP, and out-of-range, missing or incomplete data were queried by EORP to local sites.

### Statistical analysis

Descriptive data are presented with *n* (%) and median [interquartile range (IQR)] and groups were compared using non-parametric statistics. Natriuretic peptides were measured as either B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), which are not numerically comparable; therefore, in multivariable analyses, these were matched by their percentile distribution and then pooled as one variable.

In patients with AHF, length of stay and the proportion who died in hospital were assessed. Among all patients, cumulative incidence of all-cause death from enrolment (defined as date of hospital admission in AHF and date of out-patient visit) was compared in AHF vs out-patient HF and in HFrEF vs HFmrEF vs HFpEF and depicted with Kaplan-Meier curves and compared with the log rank test. For the cumulative incidence of cardiovascular (CV) death, competing risk of death from other causes was taken into account and the Aalen-Johansen estimator was calculated and groups were compared with the Gray test. Unknown cause of death was counted as CV death and also reported separately. Univariable (unadjusted), age- and sex-adjusted, and multivariable (adjusted) Cox regressions and cumulative incidence function regressions were performed to assess the crude and independent association between AHF vs out-patient HF and between the three EF categories and all-cause mortality and CV mortality. The unadjusted hazard ratios (HRs) provide information about actual risk in the specific patient category. This might be useful from an epidemiological or trial design perspective. The adjusted HRs provide information about how much of the risk is explained by the specific category, rather than by associated confounders such as age and sex, and additionally other measured clinical confounders. This might be useful when seeking to understand the potential causal, mechanistic or biological contribution of a specific category to the risk of an outcome. In the age- and sex-adjusted Cox model and cumulative incidence function model, age was modelled as splines and age × sex interaction term was included. This interaction term was non-significant in all age- and sex-adjusted analyses. Therefore, in the fully adjusted models, the age × sex interaction term was not included. The multivariable Cox regressions were performed with adjustment for 14 clinically relevant covariates (listed in the legend to Figure 2). Natriuretic peptides, unlike the other covariates, were missing in a meaningful proportion of patients. Therefore, a sensitivity analysis was conducted excluding natriuretic peptides from the multivariable Cox regressions. For Cox regressions, assumption of proportional hazards was tested with the Schoenfeld residuals and for cumulative incidence function regressions, with calculation of interaction between covariable and time.

Outcomes were also assessed as event rates per 100 patient-years of follow-up and presented with 95% confidence intervals (CIs) using Poisson models. This was done unadjusted and adjusted for age and sex.

The outcome dates were assessed for death but not for hospitalization. Therefore, the time to first hospitalization was not assessed. However, the total number of days of hospitalizations during the total number of days of follow-up was assessed.

Finally, 1-year mortality probability with 95% CIs were assessed in unadjusted, adjusted for age, sex and age  $\times$  sex interaction, and fully adjusted models.

All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 4.3.0

## Results

### Baseline characteristics

Between 1 November 2018 and 31 December 2020, 10,162 patients were enrolled from 220 centres in 41 countries. Among 10 162 patients, 32 patients (0.3%) had unknown information on setting of enrolment (AHF vs out-patient HF), leaving 10 130 patients for the AHF vs out-patient HF analyses, 39% enrolled with AHF and 61% as out-patient HF. EF was missing in 111 patients (1.1%), leaving 10 051 for EF category analyses and was categorized as reduced (HFrEF, 58%), mildly reduced (HFmrEF, 17%), or preserved (HFpEF 25%).

Table 1 shows selected baseline characteristics (more details on baseline characteristics are available in the baseline manuscript.<sup>12</sup>) Compared with out-patient HF, patients with AHF were older, slightly more commonly women, and had lower EF, higher New York Heart Association (NYHA) class, higher blood pressure (except those who died in-hospital, who instead frequently had hypotension), distinctly higher heart rate, lower estimated glomerular filtration rate, approximately 2–4 fold higher natriuretic peptide levels, and more comorbidities. Each of the common HF signs and symptoms were present in a majority of patients with AHF (and even more commonly in those who died in hospital), but only in a minority of patients with out-patient HF. There was minimal missing data, on the order of 1% for most variables, but NT-proBNP was unavailable in 49% and BNP in 83%, suggesting at least one-third of patients did not have natriuretic peptides assessed.

### Hospital course and in-hospital mortality (for patients enrolled with AHF)

Among patients with AHF ( $n = 3913$ , 39%), 5.1% died in-hospital; (Figure 1 shows percentages for HFrEF, HFmrEF, and HFpEF separately). The median (IQR) duration of hospitalization was 9 (6–14) days overall, 8 (4–18) days for those who died in hospital, and 9 (6–13) days for those discharged alive.

### Mortality and CV mortality over 1-year follow-up

Among patients with AHF, 36% survived to discharge but were lost to follow-up, and 59% had complete follow-up. Among patients with out-patient HF, 26% were lost to follow-up and 74% had complete follow-up. Among patients with complete follow-up (i.e. did not die in hospital and were not lost to follow-up), the follow-up time was 376 (360–432 days), and overall, 11% died (after AHF discharge: 20%; after out-patient visit: 6.2%).

For all-cause mortality and CV death, cumulative incidence curves, 1-year percent death/CV death, and HRs (95% CI) in unadjusted and adjusted analyses for different comparisons and different outcomes are shown in Figure 2. Overall survival was distinctly worse after discharge from AHF vs after an out-patient HF visit (Figure 2A). This difference was about half after full adjustment. Overall survival was

significantly worse in HFrEF vs HFpEF in unadjusted analysis but this was no longer significant after full adjustment. Overall survival in HFmrEF vs HFpEF was no different in unadjusted analysis but nominally worse in HFmrEF after adjustment (Figure 2B).

For CV death, the HRs for AHF vs out-patient HF were roughly similar as for all-cause death, i.e. AHF vs out-patient HF was associated with a similar excess risk ( $\sim$ 2-fold) of both all-cause death and CV death (Figure 2C). Comparing EF categories, the excess risk with HFrEF was greater for CV death than for all-cause death. Unadjusted risk was greater for HFrEF vs HFpEF, but not for HFmrEF vs HFpEF. After adjusting for covariates, HFrEF vs HFpEF remained significantly or near significantly associated with risk of CV death, and HFmrEF vs HFpEF became significantly or near significantly associated with increased risk (Figure 2D).

### Event rates for mortality and causes of death and for total HF hospitalizations

Figures 3A provides unadjusted event rates with 95% CIs per 100 patient-years of follow-up for numerous relevant outcomes. Rates of death from any cause per 100 patient-years of follow-up ranged from 3.9 to 22 depending on AHF vs out-patient status and EF category. CV death was  $\sim$ 3-fold more common than non-CV death, and more dominant with lower EF. Unknown cause of death was relatively common, and if unknown cause of death were assigned to CV causes, then CV causes of death would be  $\sim$ 4-fold more common than non-CV. Rates of total HF hospitalizations ranged from 16 to 56 and rates of total HF hospitalizations or CV death ranged from 19 to 69 per 100 patient-years, depending on AHF vs out-patient status and EF category. Figure 3B provides the corresponding event rates adjusted for age and sex.

### Number of HF hospitalizations and dispersion

Overall, about two-thirds of patients did not experience a (re-)hospitalization for HF during the 1 year of follow-up. The proportion of patients who experienced zero, 1, 2, 3, or  $>$ 3 HF (re-)hospitalizations are depicted in Figure 4. At least one (re-)hospitalization for HF was experienced in 44% AHF HFrEF, 42% AHF HFmrEF, 36% AHF HFpEF, 21% out-patient HFrEF, 14% out-patient HFmrEF, and 18% out-patient HFpEF.

## Discussion

Characteristics, treatment, and outcomes of patients with HF have been assessed in multiple epidemiological, registry-based, and cohort-based analyses and trial datasets. However, each of these are limited by lack of clinical data (internal validity), generalizability (external validity), and/or comprehensiveness (e.g. did not include acute and out-patient HF, all EF categories, chronic and new-onset HF, and multiple variable domains [demographics, clinical, laboratory, imaging, therapy, and cause specific outcomes]). The present co-primary analysis describing outcomes in over 10 000 patients of the ESC HF III Registry meets all these criteria. In-hospital mortality was 5.1% (and greater with lower EF). Among hospital survivors and out-patients over 1 year of follow-up, event rates per 100 patient-years varied for death, 3.9–22, CV death 1.7–13, and unknown cause of death 0.8–6.3. The percent of patients that were (re-)hospitalized for HF at least once over 1-year follow-up ranged 14–44% and was twice as high post-AHF compared with post-out-patient visit (Structured Graphical Abstract).

**Table 1** Baseline characteristics at enrolment

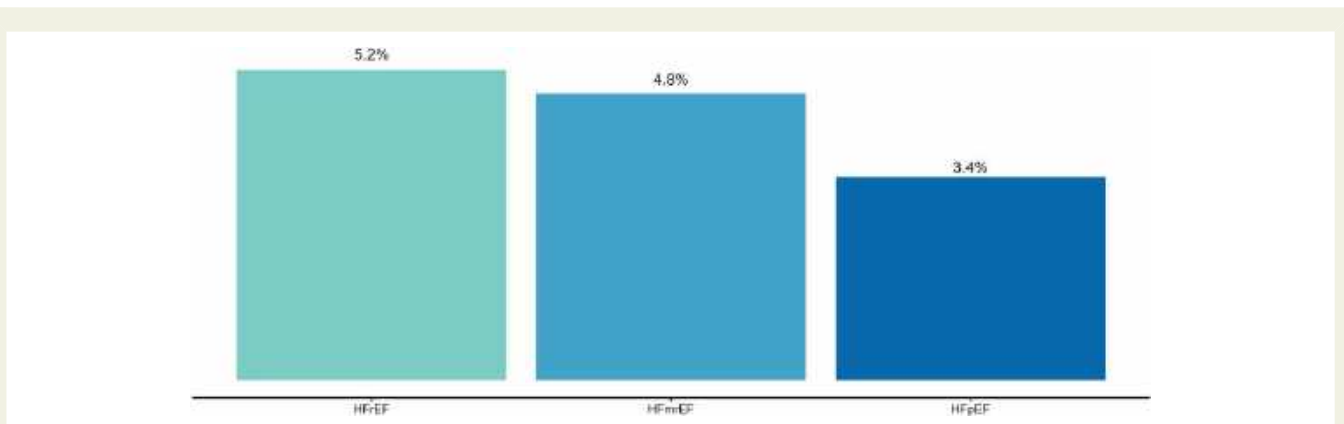
EF category	Died in hospital (n = 200/3913; 5.1%)	AHF with follow-up (n = 2294, 59%)	AHF lost to follow-up (n = 1419, 36%)	Out-patient with follow-up (n = 4597/6217, 74%)	Out-patient lost to follow-up (n = 1620, 26%)	Missing data (%)
Total n = 10 130 <sup>a</sup>						1.1
HFpEF	68%	59%	63%	54%	61%	
HFmrEF	13%	13%	13%	21%	14%	
HFpEF	19%	28%	24%	25%	25%	
Age (years)	72 (63–82)	71 (62–79)	69 (61–78)	66 (58–75)	66 (57–75)	0.0
Females	29%	37%	35%	34%	31%	0.1
BMI (kg/m <sup>2</sup> )	26 (23–29)	27 (24–31)	28 (25–32)	28 (25–31)	27 (25–30)	4.4
NYHA class III-IV	92%	81%	77%	33%	28%	1.7
Primary underlying HF aetiology						2.0
Ischaemic	56%	49%	52%	51%	54%	
Dilated cardiomyopathy	11%	13%	13%	17%	18%	
Other	33%	37%	35%	32%	28%	
Medical history						
Myocardial Infarction	46%	37%	41%	37%	42%	0.5
Stroke/transient ischaemic attack	15%	8%	10%	8.8%	9.2%	0.5
Atrial fibrillation	32%	38%	36%	28%	26%	0.6
Permanent/Persistent	16%	13%	13%	11%	12%	
Paroxysmal						
Diabetes						0.7
Yes, non-insulin treated	22%	21%	22%	21%	20%	
Yes, insulin treated	20%	16%	16%	11%	11%	
Arterial Hypertension	73%	73%	71%	65%	65%	0.5
Peripheral vascular disease	18%	14%	14%	11%	12%	1.0
Venous Thromboembolism	6.1%	3.8%	3.6%	2.6%	2.7%	0.5
CRT	7.4%	4.8%	4.0%	8.9%	11%	1.5
ICD	8.5%	8.9%	5.8%	17%	15%	1.5
Non-cardiovascular conditions	40%	30%	34%	27%	24%	1.2
Chronic obstructive pulmonary disease	14%	15%	14%	11%	10%	1.2

Continued

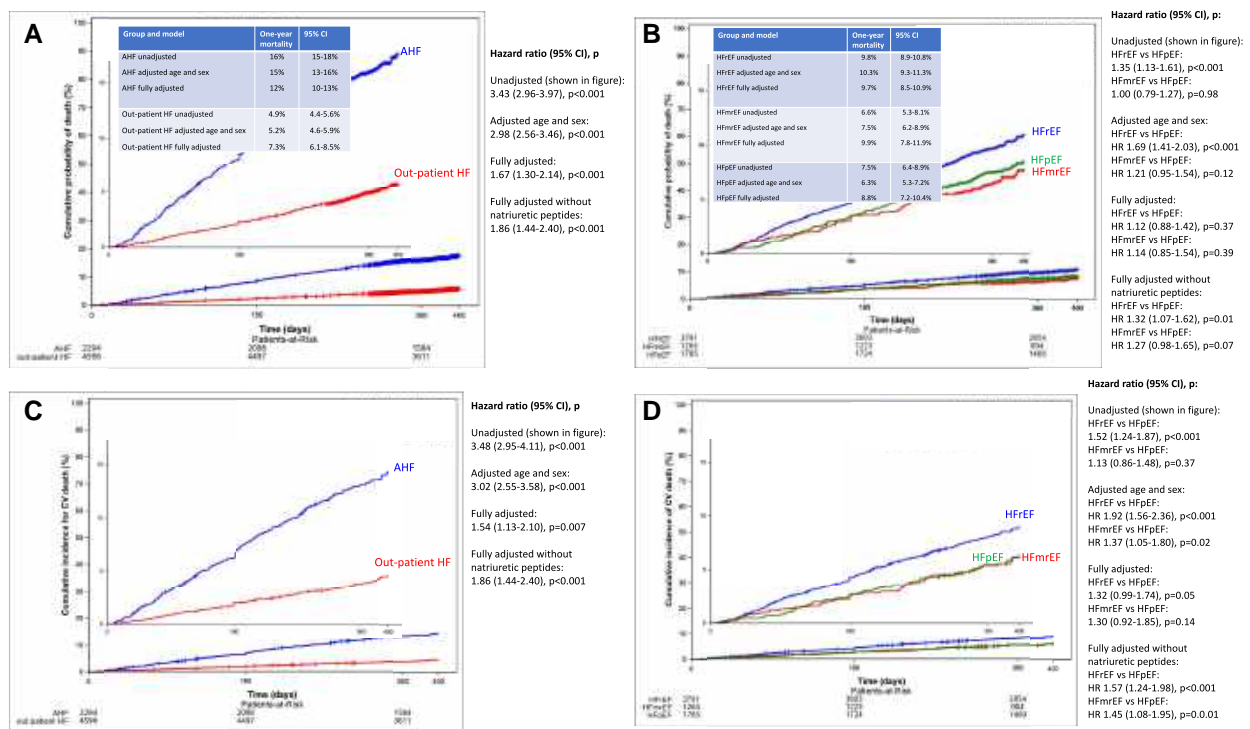
Table 1 Continued

	Died in hospital (n = 200/3913; 5.1%)	AHF with follow-up (n = 2294, 59%) 36%	AHF lost to follow-up (n = 1419, 74%) 36%	Out-patient with follow-up (n = 4597/6217, 74%)	Out-patient lost to follow-up (n = 1620, 26%)	Missing data (%)
Total n = 10 130 <sup>a</sup>						
Dialysis	3.6%	1.1%	1.5%	1.4%	1.2%	1.2
Hepatic dysfunction	8.2%	3.7%	6.0%	3.6%	2.2%	1.2
Current active cancer	6.2%	3.8%	2.9%	2.9%	1.8%	1.2
Depression	6.7%	4.8%	6.6%	5.6%	5.2%	1.2
Cognitive dysfunction	8.8%	4.2%	7.9%	1.9%	2.6%	1.2
Rheumatoid arthritis	2.1%	1.3%	1.1%	1.2%	1.2%	1.2
Sleep apnoea	2.6%	3.9%	4.6%	5.4%	3.8%	1.4
Signs, symptoms at presentation						
Systolic blood pressure (mmHg)	110 (90–135)	130 (110–150)	128 (110–145)	122 (110–139)	122 (110–140)	1.3
Systolic blood pressure ≤110 mmHg	55%	26%	30%	28%	29%	1.3
Diastolic blood pressure (mmHg)	70 (60–80)	80 (70–90)	80 (70–90)	75 (65–80)	75 (69–80)	1.5
Heart rate (bpm)	95 (76–110)	87 (74–101)	86 (72–100)	70 (63–80)	70 (65–80)	1.0
Pulmonary rales	84%	69%	64%	19%	16%	1.3
Peripheral oedema	68%	68%	60%	26%	23%	1.1
Dyspnea at rest	82%	67%	62%	14%	13%	1.0
Orthopnea	72%	57%	50%	14%	11%	1.4
Jugular venous pulse >6 cm	56%	36%	32%	12%	12%	5.2%
Laboratory at presentation						
Haemoglobin (g/dL)	11.9 (10.1–13.7)	13.0 (11.3–14.4)	12.8 (11.3–14.2)	13.4 (12.2–14.7)	13.4 (12.1–14.6)	9.8
eGFR (mL/min/1.73 m <sup>2</sup> )	43 (26–60)	55 (39–74)	55 (38–74)	66 (49–84)	64 (48–82)	10
Potassium (mmol/L)	4.3 (3.9–4.9)	4.3 (3.9–4.7)	4.3 4.0–4.7)	4.5 (4.2–4.8)	4.4 (4.1–4.8)	12
BNP (pg/mL)	1108 (760–3457)	860 (400–1945)	800 (255–1870)	400 (188–641)	432 (189–1035)	83
NT-proBNP (pg/mL)	9005 (2977–21 340)	3838 (1359–10 156)	3666 (1127–8970)	1072 (465–2604)	1221 (572–2929)	49
NT-proBNP >1000 pg/mL	93%	81%	78%	52%	58%	49

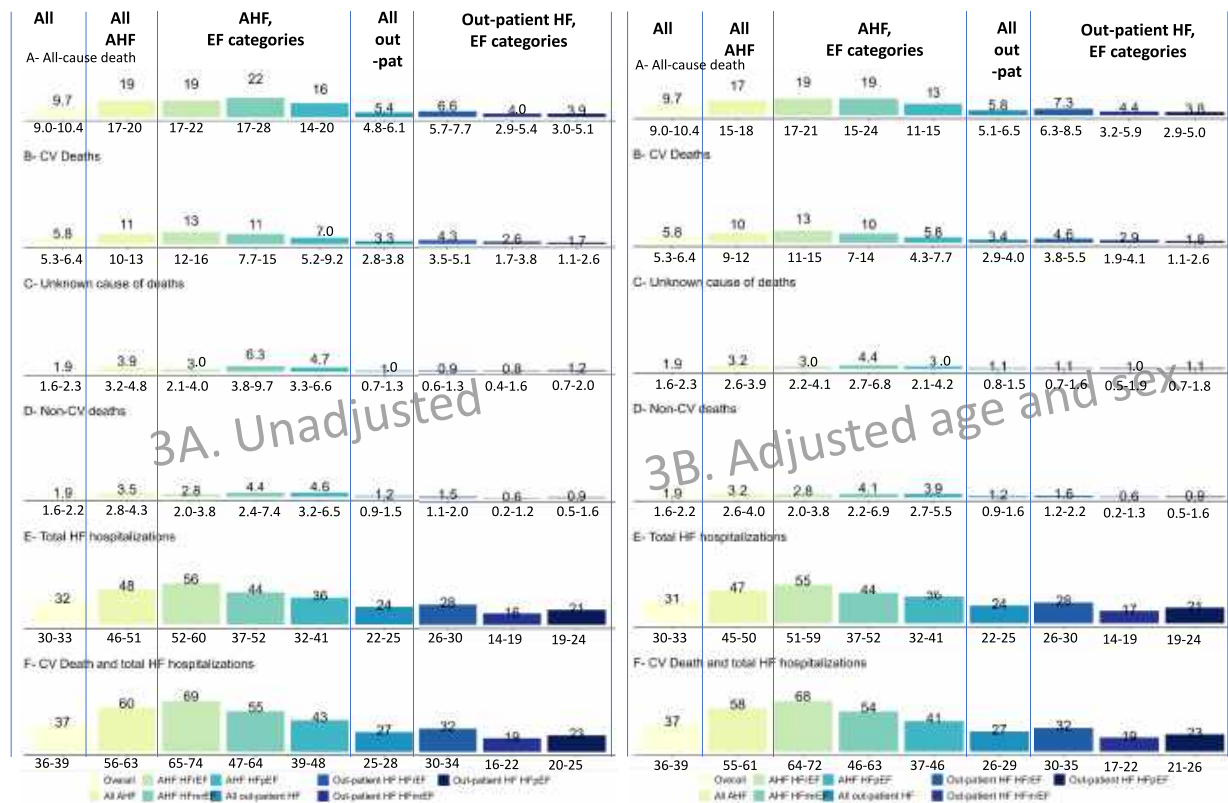
<sup>a</sup>n enrolled = 10 162 but n = 32 unknown if enrolled as AHF or out-patient; therefore n = 10 130 in Table 1. Data are at hospital admission in AHF and at or most recent before out-patient visit. Data are median (interquartile range) or percent. AHF = acute heart failure; EF = ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; IQR = interquartile range; BMI = body mass index; NYHA = New York Heart Association; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; eGFR = estimated glomerular filtration rate; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.



**Figure 1 AHF: In-hospital mortality rates.** Among patients enrolled with AHF ( $n = 3913$ , 39%), percent in-hospital mortality for HFrEF, HFmrEF, HFpEF. The overall in-hospital mortality was 5.1%. The duration of hospitalization (length of stay) was 9 (6–14) days overall, 8 (4–18) days in those who died during hospitalization, and 9 (6–13) days in those who were discharged alive



**Figure 2 A: All-cause mortality in AHF vs out-patient HF (all EF categories combined).** Patients lost to follow-up were excluded. In AHF, patients who died in hospital were excluded, and survival time is counted from time of hospital admission (baseline). Censoring occurred at last follow-up alive. The curves show cumulative incidence of all-cause death, unadjusted. The insert represents the same curves on a different scale. The inserted table shows percent 1-year mortality. Hazard ratios unadjusted include all patients not lost to follow up. Hazard ratios adjusted age and sex include age, sex and the age  $\times$  sex interaction term. Hazard ratios fully adjusted are after adjustments for 14 covariates: age, sex, EF as continuous variable, previous hospitalization for HF, BMI, NYHA class (four levels), ischaemic aetiology yes/no, diabetes yes/no, systolic blood pressure, heart rate, number of symptoms (0–4 of rales, oedema, dyspnea at rest, orthopnea), haemoglobin, eGFR, natriuretic peptides; patients with missing data on any of these variables were excluded. A sensitivity analysis was performed adjusting for the same covariates except natriuretic peptides. 2B: All-cause mortality in HFrEF vs HFmrEF vs HFpEF (AHF and out-patient HF combined). Methods are as in [Figure 2A](#) (expect adjustment is for AHF vs out-patient status rather than EF). 2C: Cumulative incidence curve for CV death in AHF vs out-patient HF (all EF categories combined). Unknown cause of death was counted as CV death. Censoring occurred at non-CV death or last follow-up alive. Methods are as in [Figure 2A](#) except models are cumulative incidence functions rather than Cox models. 2D: Cumulative incidence curve for CV death in HFrEF vs HFmrEF vs HFpEF (AHF and out-patient HF combined). Methods are as in [Figure 2C](#)



**Figure 3** Event rates (95% CI) per 100 patient-years for numerous relevant outcomes in different combinations of EF category and AHF vs out-patient HF. Numbers are number of events per 100 patient-years of follow-up and ranges are 95% CIs. Patients with AHF who died during hospitalization and patients lost to follow-up are excluded. For patients with AHF who survived discharge, time is counted from day of admission (baseline). [Figure 3A](#) shows unadjusted event rates and [Figure 3B](#) shows event rates adjusted for age and sex

## In-hospital outcomes in AHF

In AHF, in-hospital mortality was 3.4–5.2%, greater with lower EF. This was similar to the 4% in the US ADHERE Registry from 2003,<sup>13</sup> and, notably, worse than the 2.2–3.4% in the previous ESC HF Registry,<sup>14</sup> with a range 2–12%, higher with more comorbidities<sup>15</sup> and worse congestion/perfusion status.<sup>16</sup> AHF continues to lack evidence-based therapy, and it is possible that patients admitted to hospital have more severe HF in the recent era, when many patients with worsening HF who in the past might have been hospitalized are now managed with intravenous therapy but in the ambulatory setting.<sup>17</sup> HF trials more recently have included patients with AHF but only after they have been stabilized in hospital and generally after transitioning to oral diuretics.<sup>18</sup> Thus, new interventions and trials in patients with AHF still needing acute, intravenous treatment are sorely needed.

## One-year outcomes after AHF discharge and out-patient HF visit

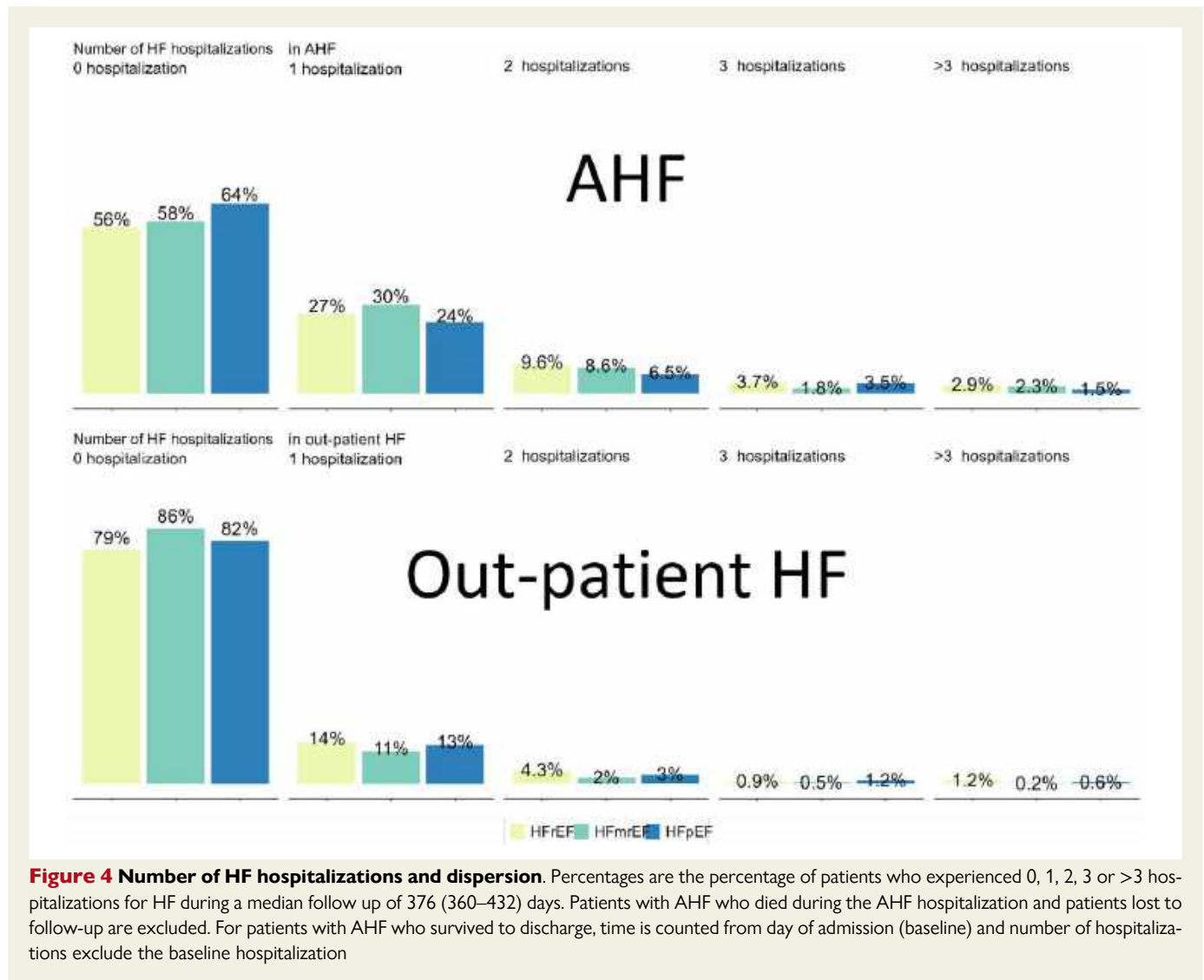
The incidence of HF is decreasing, likely because of improved recognition and management of risk factors.<sup>4</sup> However, the prevalence is increasing,<sup>4</sup> and there have been concerns that outcomes in HF are not improving, especially in the USA,<sup>19</sup> despite improved evidence-based therapy. In recent years, outcomes do seem to be improving at

least in Europe.<sup>20,21</sup> In the present analysis, enrolling patients in 41 European or ESC affiliated countries between 2018 and 2020, the risk of HF hospitalization, CV death, and all-cause death remained considerable but was lower than in previous ESC HF registries.<sup>14,22</sup> Outcomes are highly variable globally, with generally better outcomes in higher income countries.<sup>17,23</sup>

Patients discharged after AHF have a high risk of re-hospitalization and death. In the present analysis, the crude risk of HF re-hospitalization was twice as high compared with after an out-patient visit. The crude risk of both CV death and all-cause death was more than 3-fold after AHF discharge compared with after an out-patient visit. After multivariable adjustment, this risk was reduced to 50% higher, suggesting that the post discharge risk is explained by HF itself being more advanced or severe but also associated with other risk factors. After multivariable adjustment without natriuretic peptides, the risk was nearly 100% greater, suggesting that natriuretic peptides alone, as a marker of congestion and severity of HF, explain a substantial amount of the risk in HF.

## One-year outcomes in HFrEF vs HFmrEF vs HFpEF

Differences between EF categories continue to be debated.<sup>24,25</sup> Although there is considerable overlap, most data suggest that



HFmrEF is milder than but otherwise similar to HFrEF, where both are generally the result of primary myocardial injury.<sup>3,26</sup> In contrast, HFpEF appears to be a different syndrome, secondary to comorbidity-driven systemic inflammation and progressive fibrosis and cardiomyocyte changes.<sup>27</sup> Indeed, the 2021 ESC guidelines state that 'patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF', and recommend considering neuro-hormonal antagonists and modulators in HFmrEF but not in HFpEF.<sup>6</sup> Since 2021, SGLT2 inhibitors and the non-steroidal mineralocorticoid receptor antagonist finerenone have proven effective in both HFmrEF and HFpEF, perhaps because they target inflammation and fibrosis.

In the present analysis, as expected, HFrEF had greater risk of CV death, death, and HF (re-) hospitalization than HFmrEF and HFpEF, even after extensive adjustment, suggesting that low EF itself is not only a risk marker but also a risk factor. HFmrEF and HFpEF had similar risk in crude analysis, but after adjustment, HFmrEF had greater risk, again confirming that the lower EF, even if only mildly reduced, is a risk factor, and that risk in HFpEF is more driven by covariates which are 'adjusted away' in multivariable analyses.

### Event rates per 100 patient-years over 1-year follow-up

Observational clinical research commonly expresses outcomes with Kaplan-Meier curves with time to first event and percent risk. However, in order to more comprehensively quantify event rates, to compare different outcomes in different patient categories and sub-groups, and to perform power calculations for interventional trials, event rates per 100 patient-years are more useful. The present analysis is unique in its broad inclusion of patients from 41 European and ESC-affiliated countries, making it generalizable and suitable for estimating event rates for trialists planning future randomized controlled trials in Europe. Furthermore, it is unique in its concurrent and comparative assessments of both acute and out-patient HF, both *de novo* and pre-existing HF, and all three EF categories. Thus, this analysis may serve as reference material for what to expect when including different patient categories and studying different outcomes, although, despite various enrichment criteria, clinical trials end up enrolling patients with lower event rates than registries and cohorts, both because of formal exclusion criteria of patients with e.g. cancer, and because of conscious or un-conscious selection bias among investigators towards younger and healthier patients.<sup>28</sup>

The present analysis presents event rates for the different patient categories for six different CV and non-CV outcomes. A few observations are especially important: markers associated with greater event rates such as acute vs out-patient HF and lower EF were largely expected but were also generally associated with both CV and competing non-CV outcomes, with the exception of lower EF actually being associated with lower risk of non-CV death. It would be helpful but remains difficult to identify risk markers other than e.g. EF which are associated with HF and CV events but not with all-cause or even non-CV events. From CV deaths alone to the composite of total CV deaths and HF hospitalizations, and in the different patient categories, event rates had an extremely wide range, from 1 to 69 per 100-patient-years, suggesting the statistical power of trials will vary extensively based on selection criteria. The rate of CV death in out-patient HFpEF was only 1.7 per 100 patient-years, providing exceedingly low power to detect a treatment effect on CV death in out-patient HFpEF. The rate in out-patient HFrEF was also low, at 4.3 per 100 patient-years, suggesting that a treatment effect on CV death in a HFrEF clinical trial would require a substantial portion enriched for advanced HFrEF and/or post AHF. Rates of HF (re-)hospitalization on the other hand were quite high suggesting novel interventions can still have substantial and clinically meaningful effects.

## Limitations

The ESC HF III Registry has broad European and ESC-affiliated coverage but participating sites are cardiology oriented and may not be representative of HF in internal medicine, geriatrics or primary care settings. This is indeed suggested by the relatively young age of patients, better use of GDMT in this ESC HF III Registry<sup>12</sup> than in other more generalizable cohorts and registries or general populations,<sup>29,30</sup> and relatively low event rates compared with population-based cohorts, especially in HFpEF, where many patients with higher age and more comorbidities may not be seen in cardiology departments. Use of natriuretic peptides was low. There were no mandated diagnostics or treatments in the protocol. Most patients had chronic HF and thus already a diagnosis established. Although repeat natriuretic peptide testing is common, their main value is for diagnosis, and investigators may not have considered repeat measurements clinically necessary or indicated. Surprisingly many patients were lost to follow-up, which is unlikely to occur at random but more commonly in older, frailer patients with higher mortality. In contrast to in a randomized controlled trial, there were no mandatory regular follow-up visits. A visit, contact or attempted contact at 12 months was specified in the protocol, but may have been difficult in older patients and at referral centres who may not follow patients continuously. Thus, the present results may underestimate true event rates during follow-up, particularly in older patients with HFpEF. Outcome collection during follow-up included death, cause of death, and date of death, allowing time to event analyses, and number of hospitalizations and causes of hospitalization, but not time to hospitalization, precluding time to first HF (re-) hospitalization or to the commonly used time to composite of first CV death or HF hospitalization event.

## Conclusions

The present analysis combines granular data for clinical characterization and for multivariable adjustment when assessing outcomes, providing internal validity and reliability, with large sample size and broad European and ESC-affiliated coverage, providing external validity and generalizability. It reports both in-hospital and 1-year post-discharge outcomes in AHF, and 1-year outcomes in out-patient HF, includes

**Table 2** Potential uses of ESC HF III Registry data

Potential uses of ESC HF III Registry data	
Data	Potential use
Patient characteristics	<ul style="list-style-type: none"> <li>• Epidemiological studies</li> <li>• Ejection fraction category comparisons</li> <li>• Resource allocation</li> <li>• Patient phenotyping, cluster analyses, machine learning, artificial intelligence</li> <li>• Trial design</li> </ul>
Treatment	<ul style="list-style-type: none"> <li>• Implementation science</li> <li>• Resource allocation</li> <li>• Cost-effectiveness studies</li> <li>• Education and awareness</li> <li>• Screening</li> <li>• Registry-based randomized controlled trial infrastructure and design</li> </ul>
Cause-specific outcomes	<ul style="list-style-type: none"> <li>• Epidemiological studies</li> <li>• Resource allocation, targeting and prioritizing treatment</li> <li>• Cost-effectiveness studies</li> <li>• Ejection fraction category comparisons</li> <li>• Patient phenotyping, cluster analyses, machine learning, artificial intelligence</li> <li>• Competing risk analyses</li> <li>• Trial design</li> </ul>
Event rates	<ul style="list-style-type: none"> <li>• Trial design</li> </ul>

both *de novo* and pre-existing HF, and reports multiple relevant cause-specific outcomes and comparisons among all three EF categories. These data are useful for patient care and future trials and for all stakeholders working to improve outcomes in patients with HF (Table 2).

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## Supplementary data

Supplementary data are not available at [European Heart Journal](https://eurheartj/advance-article/doi/10.1093/eurheartj/ehaf1074/8494560) online.

## Declarations

### Disclosure of Interest

There are no conflicts of interest related to the ESC HF III Registry or to this manuscript. Outside of the submitted work, there are the following disclosures: Lars H. Lund declares grants or contracts from AstraZeneca, Vifor Pharma, Novartis, Boston Scientific, and

Boehringer Ingelheim; consulting fees for trial design and/or development/implementation strategy from Merck, Vifor Pharma, AstraZeneca, Bayer, Pharmacosmos, Medscape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, and Servier; Payment or honoraria for lectures from Abbott, Medscape, Radcliffe, AstraZeneca, and Novartis. He also serves on the Board of the Heart Failure Association of the ESC, the Board of the Swedish Society of Cardiology, HF Working Group and is as a Fellow of the ESC. He reports holding stock in AnaCardio. Maria Generosa Crespo-Leiro declares grants or contracts from AstraZeneca and Vifor Pharma; consulting fees from Medtronic and Takeda; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim, Novartis, AstraZeneca, Vifor Pharma, CareDx, Astellas, Abbott, Medtronic, and Bayer; and support for attending meetings and/or travel from Novartis and Abbott. Eleonora B. Vataman declares payments made to her for honoraria for lectures and/or educational materials/events from Berlin Chemie AG, and Johnson & Johnson; consulting fees for Egis Pharma. Hamayak Sisakian declares payment as honoraria for lectures, presentations and travel grants from Berlin Chemie AG, Servier, KRKA; Support for attending meetings and/or travel for Servier, Berlin Chemie. Stefan D Anker declares Grants or contracts (CSL/Vifor, Grants for IITs (Fair-HF2, Fair-HFpEF). Abbott, Grants for IIT (Reshape-HF2)); Consulting fees (Actimed Therapeutics, Advisory board; Alleviant, Ad-hoc consultancy, Astra Zeneca, Ad-hoc consultancy; Berlin Heals, Ad-hoc consultancy; Brahms, Ad-hoc consultancy; Cordio, Ad-hoc consultancy; Cytokinetics, Ad-hoc consultancy; Edwards, Ad-hoc consultancy; Lilly, Advisory board; Mankind Pharma, Advisory board; Novo Nordisk, Ad-hoc consultancy; Regeneron, Ad-hoc consultancy; Relaxera, Advisory board; Repairon, Advisory board; Scirent, Ad-hoc consultancy; Sensible Medical, Ad-hoc consultancy; Vectorious, Ad-hoc consultancy, Vivus, Advisory board; Patents planned, issued or pending Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (Abbott, Fees for Covid19 advisory board work; Bayer AG, Trial steering committee work & consultancy; Boehringer Ingelheim, Trial steering committee work & consultancy; Cardiac Dimensions, Trial steering committee work & consultancy; Cardior, Trial committee work & consultancy, CVRx, Trial steering committee work; Impulse Dynamics, Trial steering committee work, Medtronic, Trial steering committee work; Occlutech, Trial steering committee work & consultancy, Pfizer, Trial steering committee work; Vifor/CSL, Trial/registry steering committee work & consultancy; V-Wave, Trial steering committee work & consultancy. Ovidiu Chioncel reports support for attending events and or meetings Servier and Boehringer Ingelheim. Gerasimos Filippatos reports lecture fees and/or advisory and/or trial committee membership by Bayer, Boehringer Ingelheim, Servier, Novartis; Research Grants from the European Union; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid (Heart Failure Association; Jacc Heart Failure; European Journal H.F); Other financial or non-financial interests (Medtronic, trial committee membership fees; BAYER, trial committee membership fees; Boehringer Ingelheim, trial committee membership fees; Vifor, trial committee membership fees; Amgen, Committee Member; Servier, trial committee membership fees; Impulse Dynamics, trial committee membership fees; Cardior, consulting fee; Novonordisk, consulting). Mitja Lainscak declares Grants or contracts (Slovenian Research and Innovation

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Radcliffe Group, Stiftung Pfizer Forschungspreis, Vifor. Prof. Ruschitzka has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years. Remuneration for following lectures were made directly to the University of Zurich and do not impact on Prof. Ruschitzka's personal remuneration: Abbott, Amgen, AstraZeneca (A+Science AB), Bayer (At the Limits), Boehringer Ingelheim, Boston Scientific (CCE Services), Brigham and Women's Hospital Boston, C.T.I GmbH, Davos Congress, FomF, Hôpitaux Universitaires des Genève (GECORE), Luzerner Kantonsspital, Sanofi-Aventis, Servier, Medcon, Medscape (WebMD), Medtronic, Medworld, Novartis, Roche, Ruwag, Swiss Heart Failure Academy, The Hong Kong Heart Failure Society, Trama Solutions SL, Inselspital Bern, Charité—Universitätsmedizin Berlin (Medical Education Global Solutions), Romanian Society of Cardiology, ÖKG Österreichische Gesellschaft für Kardiologie, Zoll. He declares Support for attending meetings and/or travel from AstraZeneca (IMC/A+Science AB), Boehringer Ingelheim, Centro Hospitalar de Vila Nova de Gaia, C.T.I. GmbH (Universitätsklinikum Düsseldorf), European Society of Cardiology, Monocle, Novartis, Spektar Putovanja, Austrian Heart Failure Association, Heart Failure Association of the ESC. Prof. Ruschitzka has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years. Remuneration for following Advisory Boards were made directly to the University of Zurich and do not impact on Prof. Ruschitzka's personal remuneration: Bayer: HF Expert Summit, Advisory Board Meeting. Roche: Advisory Board Meeting IMC/AstraZeneca: Advisory Board Meeting Amgen: Advisory Board Meeting. Gianluigi Savarese declares grants or contracts from CSL Vifor, Pharma, Novartis, Boehringer Ingelheim, Boston Scientific, AstraZeneca, Pharmacosmos, Merck, Bayer, Cytokinetics, Medtronic, Servier; Consulting fees from TEVA, AstraZeneca, Medical Education Global Solutions, Atheneum, Genesis, CSL Vifor, Servier, Translational Medicine Academy Foundation (TMA); Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events Novartis, Roche, Cytokinetics, Hikma, Medtronic, Pharmacosmos, AstraZeneca, Menarini, CSL Vifor Pharma, INTAS, GETZ; Support for attending meetings and/or travel from Boehringer Ingelheim, Servier; Participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Bayer, Edwards LifeScience, Uppsala Clinical Research Center (UCR), CSL Vifor, Servier, Abbott, Cytokinetics. Petar M. Seferović declares Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Honorarium for lecture: Boehringer Ingelheim, and Menarini). Aldo P. Maggioni received grants or contracts for participating in study committees from Novartis, Bayer, Sanofi and Astra Zeneca, outside the present work. Lucica Grigoriga declares Payment or honoraria for lectures, from Lecture fees from Astra Zeneca, Servier, Bayer, Novartis, KRKA, Amgen; Support for attending meetings and/or travel from P8zer, Astra Zeneca, Sano8, Sunwave, Servier. Theresa A McDonagh declares from Boehringer Ingelheim payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events. Belma Pojskic declares Support for attending meetings and/or travel from Farmavita, Krka. Dulce Alves Brito declares payments made to him: contracts for consultancy (participation in Advisory Boards)—Alnylam, Astra Zeneca, Bayer, Bial, Bristol-Myers Squibb, Novo Nordisk and Pfizer; Consulting fees (participation in Advisory Boards)—Alnylam, AstraZeneca, Bayer, Bial, Bristol-Myers Squibb, Novo Nordisk and Pfizer; Lecture fees from AstraZeneca, Bayer, Bial, Bristol-Myers Squibb and Pfizer; Support for attending meetings and/or travel from Astrazeneca, Bayer, Bial and Pfizer;

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## Data Availability

Direct access to the HF III Registry dataset is limited to the EORP HF III Data Management and Statistical Analysis teams. Country-specific datasets may be provided to the national cardiology societies upon request to EORP.

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## Ethical Approval

Locally appointed ethics committees approved the research protocol, and informed consent was obtained from all patients.

## Pre-registered Clinical Trial Number

Not applicable.

## APPENDIX 1. EORP Oversight Committee

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