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ORIGINAL ARTICLE

# Heart Failure with Preserved vs. Reduced Ejection Fraction: Patient Characteristics, In-hospital Treatment and Mortality—DanAHF, a Nationwide Prospective Study

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## Abstract

This study aims to describe baseline characteristics and in-hospital management of a patient cohort hospitalized with acute heart failure (AHF). Adult patients in Denmark admitted with a medical diagnosis during a 7-day period were reviewed for symptoms and clinical findings suggestive of AHF. HFpEF was defined as LVEF ≥ 45%. Of 5194 patients, 290 (6%) had AHF. Sixty-two percent ($n = 179$) was diagnosed with HFpEF. Compared to HFrEF patients, HFpEF patients were more often women (48% vs. 31%, $p = 0.004$), less likely to have ischemic heart disease (31% vs. 53%, $p = 0.002$) and a pacemaker/ICD (7% vs. 21%, $p < 0.001$/1% vs. 8%, $p < 0.001$). Fewer HFpEF patients received intravenous diuretics (43% vs. 73%, $p < 0.001$) and inotropes (2% vs. 7%, $p = 0.02$), while more HFpEF patients received nitro-glycerine (59% vs. 44%, $p = 0.02$). Intubation/NIV, ICU admission, and revascularization were used similarly. Hospitalization was shorter for HFpEF patients (4 vs. 6 days, $p < 0.001$), with no significant difference in survival to discharge (96% vs. 91%, $p = 0.07$). Of AHF admissions, nearly two-thirds was due to HFpEF. Compared to HFrEF, HFpEF patients had a lower cardiac comorbidity and a 2-day shorter hospitalization.

**Keywords** Acute Heart Failure · HFpEF · HFrEF · Treatment · Outcome

## Background

Heart failure (HF) is known to be a major cause of both morbidity and mortality, with an estimated prevalence of 1–2% in economically developed countries [1–3]. An estimation from 2014 suggested that 26 million people worldwide were living with HF [4], and that approximately half of these patients had HF with preserved ejection fraction (HFpEF) [5–7]. Studies have indicated an increase in the prevalence of patients with HFpEF, probably due to an ageing population

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[6]. It is estimated that in Europe, a total of 1–4% of all both medical and surgical admissions in developed countries are caused by HF as the primary diagnosis [8].

Guidelines for the treatment of patients with HF with reduced ejection fraction (HFrEF) are based on several randomized controlled trials [9]. Apart from the EMPEROR-Preserved Trial finding a lower incidence of hospitalization for HF among patients with HFpEF treated with empagliflozin [10], no treatment has yet been proven to significantly and efficiently improve the prognosis in patients with HFpEF [11–15]. A phenotypical heterogeneity in the HFpEF population has been proposed as a reason for studies not being able to confirm a significant effect of different treatment entities [12, 16]. A study of clearly defined subgroups might contribute to target a specific and effective treatment.

The mortality rate for patients with HF is generally high, with a worse prognosis than patients with breast, bowel, or prostate cancer [8]. When comparing mortality rates in patients with HFrEF and HFpEF, the literature is not consistent. It has been suggested that further epidemiological studies characterizing the HFpEF population are important to improve future trial designs and reduce hospitalizations and mortality in patients with HFpEF [5].

The aim of the current DanAHF sub study was to characterize a consecutive cohort of patients with preserved ejection fraction admitted to hospital with acute HF, and more specifically to compare HFpEF and HFrEF in terms of comorbidity, clinical findings, in-hospital treatment, and mortality in a nationwide study in Denmark.

## Method

### DanAHF Study Design and Data Collection

All admissions of adult patients (≥ 18 years) in Denmark with a medical diagnosis during a consecutive 7-day period in 2015 were systematically reviewed. All patient charts were individually assessed for symptoms, clinical findings, and in-hospital treatment and these findings were compared to a prespecified list of symptoms and treatment modalities suggestive of acute HF (Fig. 1). Patients were allocated 1 point for each symptom and treatment, respectively. An accumulated score of ≥ 3 points with at least one point from each category (symptoms or treatment, respectively) was included as a patient with acute HF according to the prespecified study protocol. Patients with acute HF were categorized as HFpEF or HFrEF based on the left ventricular ejection fraction (LVEF) obtained by 2D echocardiography during admission (see below). Patients without an available echocardiography were excluded from the current study ($n = 45$, 13%). Medication at the time of admission and discharge was registered using patient and medical charts.

### Definition of HFpEF

In 2016, the European Society of Cardiology introduced HF with mid-range ejection fraction (now mildly reduced ejection fraction, HFmrEF) in the HF guidelines, defined as LVEF 40–49% [9]. Until then, HF had been subdivided into only HFpEF and HFrEF, reflected in prior clinical trials. In this study, patients with acute HF were categorized in HFpEF defined as LVEF ≥ 45% and HFrEF as LVEF < 45%. This LVEF cut-off was chosen in accordance with the majority of HFpEF clinical trials to date, to ensure comparability between the current study and prior studies. Comparable studies include the TOPCAT Trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) [13], the PARAGON-HF Trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) [12], the I-PRESERVE Trial (Irbesartan in patients with heart failure and PRESERVEd ejection fraction) [17], and the Ancillary DIG Trial (Digitalis Investigation Group) [14].

### Statistics

For normally distributed data, continuous variables are presented as mean ± the standard deviation (SD), while non-normally distributed data are presented as median and interquartile ranges (Q1–Q3). Student's unpaired *t*-test or Wilcoxon's rank sum tests were applied to analyze the differences. Categorical variables are presented as number (*n*) and percentage and chi-square test were applied for the difference analyses. The statistical software SAS 9.4 was used for all analyses. All statistical tests were two-sided, and the significance level was chosen as $p < 0.05$.

### Ethics

The DanAHF study and data collection has been authorized by the Danish Health and Medicines Authorities.

## Results

A total of 5194 patients were admitted with a medical diagnosis in Denmark during the prespecified study week. Of them, 335 patients (6.4%) fulfilled the predetermined symptom and treatment criteria for acute HF. An echocardiography was available in 290 patients (87%) and patients with no available echocardiography were excluded from further analyses. A total of 179 patients (62%) were diagnosed with HFpEF and 111 patients (38%) with HFrEF.

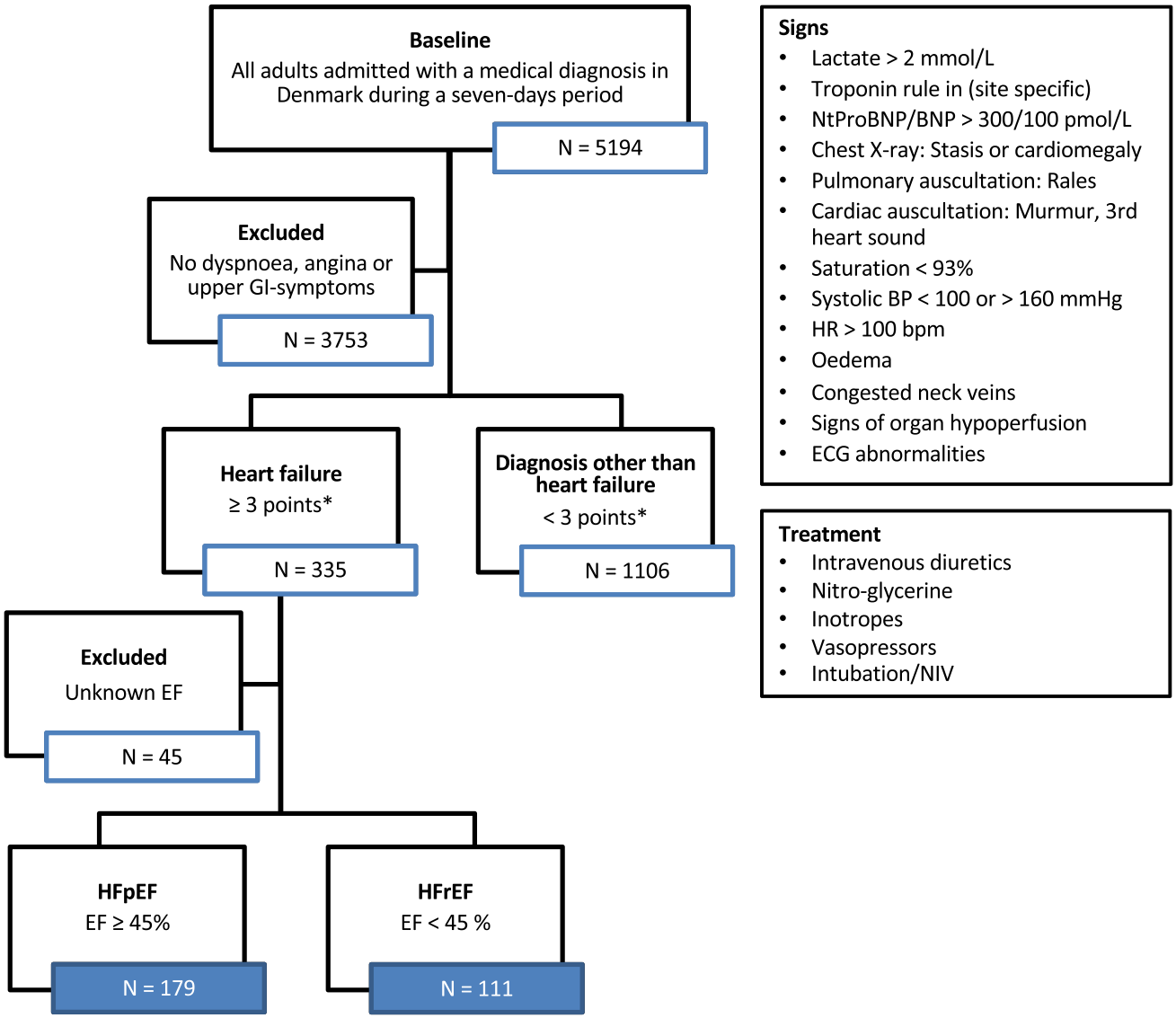


**Fig. 1** Consort diagram and point system used for diagnosing patients with acute heart failure in the DanAHF cohort. *Patients were allocated one point for each sign or treatment found in their journal. Only patients with at least one sign and one treatment were included in the heart failure group. GI, gastrointestinal; NIV, non-invasive ventilation

## Baseline Characteristics

The baseline characteristics for patients with HFpEF and HFrEF are shown in Table 1. Mean LVEF in the HFpEF group and HFrEF group were 56% (±5%) and 29% (±9%), respectively. Patients with HFpEF were more often women (48 vs. 31%, $p = 0.004$), less likely to have a past medical history of ischaemic heart disease (IHD) (31 vs. 53%, $p = 0.002$), known prior congestive HF (16 vs. 66%, $p < 0.001$), chronic kidney disease (10 vs. 23%, $p = 0.002$), and a previously implanted pacemaker or implantable cardiovert defibrillator (ICD) (7% vs. 21%, $p < 0.001$ and 1% vs. 11%, $p < 0.001$), compared to patients with HFrEF. In the HFpEF group, 28 of the 179 patients had a past medical history of HF, resulting in 151 new-onset (de novo) HF (84%), compared to 39 de novo HF (35%) in the HFrEF group. Patient with HFpEF and HFrEF was comparable with regard to age (71 vs. 72 years), body mass index (BMI) (28 vs. 27 kg/m [2]), previous history of atrial fibrillation (28% vs. 27%), hypertension (52% vs. 55%), chronic obstructive pulmonary disease (COPD) (23% vs. 19%), and diabetes (23% vs. 29%).

## Clinical Presentation

Patient with HFpEF had a significantly higher systolic blood pressure at the time of admission (141 vs. 133 mmHg, $p = 0.02$) and a significantly lower heart rate (81 vs. 92 beats

**Table 1** Comparison of baseline characteristics of patients with HFpEF and HFrEF in the DanAHF cohort

| | *N* | Whole group | HFrEF (LVEF < 45%) | HFpEF (LVEF ≥ 45%) | *P*-value (HFpEF vs. HFrEF) |
|---|---|---|---|---|---|
| Number, (%) | 335 | 335 (100) | 111 (33) | 179 (53) | < 0.001 |
| Men, *N* (%) | 188 | 188 (56) | 76 (69) | 93 (52) | 0.004 |
| Age, years (± SD) | 335 | 71.6 (± 13) | 71.9 (± 13) | 71.0 (± 14) | 0.61 |
| BMI, kg/m$^2$ (± SD) | 185 | 28 (± 7) | 27 (± 6) | 28 (± 7) | 0.45 |
| LVEF, % (± SD) | 290 | 46 (± 15) | 29 (± 9) | 56 (± 5) | < 0.001 |
| Cardiovascular history | | | | | |
| Heart failure, *N* (%) | 323 | 105 (33) | 72 (66) | 28 (16) | < 0.001 |
| Ischemic heart disease, *N* (%) | 327 | 118 (36) | 58 (53) | 54 (31) | 0.002 |
| CABG, *N* (%) | 335 | 36 (11) | 19 (17) | 15 (8) | 0.004 |
| PCI, *N* (%) | 335 | 53 (16) | 23 (21) | 26 (15) | 0.007 |
| Atrial fibrillation, *N* (%) | 331 | 84 (25) | 30 (27) | 49 (28) | 0.96 |
| Pacemaker, *N* (%) | 333 | 36 (11) | 23 (21) | 12 (7) | < 0.001 |
| ICD, *N* (%) | 335 | 13 (4) | 12 (11) | 1 (1) | < 0.001 |
| Comorbidity | | | | | |
| Hypertension, *N* (%) | 323 | 167 (52) | 59 (55) | 89 (52) | 0.64 |
| Diabetes, *N* (%) | 332 | 84 (25) | 32 (29) | 40 (23) | 0.23 |
| COPD, *N* (%) | 330 | 78 (24) | 21 (19) | 41 (23) | 0.38 |
| Active smoker, *N* (%) | 335 | 81 (24) | 25 (23) | 46 (26) | 0.14 |
| Chronic kidney disease, *N* (%) | 332 | 48 (15) | 26 (23) | 18 (10) | 0.002 |
| Stroke, % | 331 | 41 (12) | 16 (14) | 20 (11) | 0.44 |
| Cancer (%) | 331 | 38 (12) | 12 (11) | 17 (10) | 0.71 |
| Days of admission last year, days (IQR) | 331 | 5 (2–10) | 6 (4–12) | 4 (2–8) | < 0.001 |

*BMI*, body mass index; *CABG*, coronary artery bypass graft; *COPD*, chronic obstructive pulmonary disease; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *PCI*, percutaneous coronary intervention

per minute, $p < 0.001$) (Table 2). Patients with HFrEF were significantly more likely to have an abnormal ECG, rales on auscultation, jugular vein distension, and a chest X-ray with stasis or cardiomegaly. No significant difference with regard to peripheral edema was found (37% in HFpEF vs. 46% in HFrEF). Patients with HFpEF had lower levels of serum creatinine (83 vs. 100 mmol/L, $p < 0.001$, normal reference range 60–105 mmol/L) compared to patients with HFrEF, but hemoglobin and lactate levels did not differ significantly. In the HFpEF and HFrEF group, 17 (24%) and 18 (31%) patients respectively had lactate levels > 2 mmol/L.

## In-hospital Management

During the index hospital admission, significantly fewer patients with HFpEF were treated with intravenous (IV) diuretics (43% vs. 73%, $p < 0.001$), and inotropes (2% vs. 7%, $p = 0.017$) along with a borderline significant tendency towards fewer patients with HFpEF receiving vasopressors (1% vs. 4%, $p = 0.051$). Nitro-glycerine was more often administered to patients with HFpEF (59% vs. 44%, $p = 0.016$) (Table 3). Intubation or non-invasive ventilation (NIV) was used equally in both groups (8% vs. 9%, $p = 0.84$), and there was no significant difference in the percentage admitted to the intensive care unit (ICU) (10% vs. 13%, $p = 0.47$). The number of coronary angiographies (CAGs) and revascularizations (percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)) performed during admission did not differ between patients with HFpEF and HFrEF (36% vs. 34% for CAG and 62% vs. 56% for revascularization of the CAGs performed).

## Medication

Medication prescribed prior to hospital admission and at hospital discharge is shown in Table 4. Prior to hospital admission, patients with HFpEF were significantly less likely to receive treatment with diuretics (43% vs. 63%, $p = 0.001$), beta-blockers (38% vs. 59%, $p < 0.001$), ACE-inhibitors (ACEIs) (20% vs. 32%, $p = 0.032$), and aldosterone antagonists (MRAs) (5% vs. 16%, $p = 0.002$), compared to patients with HFrEF. There was no significant difference in the pre-admission treatment with anticoagulants (37% vs. 42%), platelet inhibitors (24% vs. 28%), angiotensin receptor blockers (ARBs) (13% vs. 15%), or COPD inhalers (23% vs.

**Table 2** Comparison of clinical presentation of patients with HFpEF and HFrEF in the DanAHF cohort

| | *N* | HFrEF (LVEF < 45%) | HFpEF (LVEF ≥ 45%) | *P*-value |
|---|---|---|---|---|
| Vital signs | | | | |
| Pulse, bpm (± SD) | 277 | 92 (± 28) | 81 (± 22) | < 0.001 |
| Systolic BP, mmHg (± SD) | 276 | 133 (± 32) | 141 (± 28) | 0.02 |
| Diastolic BP, mmHg (± SD) | 274 | 79 (± 18) | 78 (± 18) | 0.46 |
| Saturation < 93%, *N* (%) | 278 | 30 (28) | 40 (23) | 0.35 |
| Pulse > 100 bpm, *N* (%) | 284 | 42 (39) | 23 (13) | < 0.001 |
| Clinical findings | | | | |
| Abnormal ECG, *N* (%) | 273 | 70 (67) | 89 (53) | 0.026 |
| Chest X-ray: stasis or cardiomegaly, *N* (%) | 205 | 54 (63) | 51 (43) | 0.005 |
| Peripheral edema, *N* (%) | 261 | 45 (46) | 61 (37) | 0.18 |
| Jugular vein distension, *N* (%) | 175 | 9 (13) | 2 (2) | 0.002 |
| Lung auscultation: rales, *N* (%) | 279 | 53 (50) | 58 (34) | 0.006 |
| Heart auscultation: murmur or gallop rhythm, *N* (%) | 279 | 9 (9) | 23 (13) | 0.26 |
| Organ hypoperfusion, *N* (%) | 277 | 6 (6) | 6 (4) | 0.35 |
| Blood tests | | | | |
| Haemoglobin, mmol/L (± SD) | 285 | 7.8 (± 1) | 8.0 (± 1) | 0.46 |
| Creatinine, mmol/L (IQR) | 285 | 100 (78–148) | 83 (70–105) | < 0.001 |
| BNP > 100 pmol/L, % | 29 | 8 (53) | 5 (36) | 0.34 |
| BNP, pmol/L (IQR) | 18 | 1268 (486–6273) | 55 (29–5222) | 0.03 |
| CRP, mg/L (IQR) | 290 | 11 (4–27) | 5.5 (2–19) | < 0.001 |
| Lactate > 2 mmol/L, % | 129 | 18 (31) | 17 (24) | 0.37 |
| Echocardiography | | | | |
| LVEF, % (± SD) | 290 | 29 (± 9) | 56 (± 5) | < 0.001 |

*BNP,* B-type natriuretic peptide; *BP,* blood pressure; *BPM,* beats per minute; *ECG,* electrocardiogram; *LVEF,* left ventricular ejection fraction

18%). At discharge, the same tendency was seen with significantly fewer patients with HFpEF receiving diuretics (51% vs. 77%, $p < 0.001$), beta-blockers (58% vs. 77%, $p = 0.001$), ACEIs (22% vs. 43%, $p < 0.001$), and MRAs (10% vs. 27%, $p < 0.001$).

Comparing medication at admission and at discharge for both patients with HFpEF and HFrEF (Fig. 2), there was a significant increase in the number of patients receiving platelet inhibitors, anticoagulants, diuretics, beta-blockers, and MRAs at discharge. Only patients with HFrEF had a significant increase in ACEIs and digoxin. No significant change was seen regarding amiodarone, calcium channel blockers, ARBs, or COPD inhalers.

## Re-admission Rate and Mortality

Patients with HFpEF were generally hospitalized for a shorter period compared to patients with HFrEF, with a median duration of hospitalization of 4 vs. 6 days, respectively ($p < 0.001$). A trend towards increased in-hospital mortality in the HFrEF group was seen (7 HFpEF (3.9%) vs. 10 HFrEF (9.0%) in-hospital deaths), but no significant difference in survival to discharge was found (96% vs. 91%, $p = 0.07$).

Comparing medical readmissions for any cause during the first month after discharge, there was no significant difference (20% vs. 26%, $p = 0.2$). However, during the first year after discharge, patients with HFpEF had a significantly lower readmission rate (43% vs. 57%, $p = 0.023$). Comparing readmissions with HF as the primary diagnosis, significantly fewer patients with HFpEF were readmitted both within 1 month (3% vs. 14%, $p < 0.001$) and within 12 months (5% vs. 31%, $p < 0.001$) after discharge.

## Sensitivity Analysis

Of the 335 patients with acute HF, 45 patients had no available echocardiography and could not be included for further analysis. Comparing these 45 patients to the 290 patients with HFpEF/HFrEF, they were 2 years older and more likely to be women (58% vs. 42%, $p = 0.04$). In the group with missing echocardiography, significantly fewer had a past medical history of atrial fibrillation (12% vs. 27%, $p = 0.03$), IHD (14% vs. 39%, $p = 0.002$), and HF (13% vs. 35%, $p = 0.005$) compared to the HFpEF/HFrEF group. A past medical history of COPD was significantly more common in patients with a missing echocardiography (37% vs. 22%, $p = 0.03$) and likewise with regard to cancer (21% vs.

**Table 3** Comparison of in-hospital management and readmission status of patients with HFpEF and HFrEF in the DanAHF cohorte

| | *N* | HFrEF (LVEF < 45%) | HFpEF (LVEF ≥ 45%) | *P*-value |
|---|---|---|---|---|
| IV diuretics, *N* (%) | 289 | 81 (73) | 77 (43) | < 0.001 |
| IV nitro-glycerine, *N* (%) | 290 | 49 (44) | 105 (59) | 0.016 |
| Inotropes, *N* (%) | 290 | 8 (7) | 3 (2) | 0.017 |
| Vasopressors, *N* (%) | 289 | 4 (4) | 1 (1) | 0.051 |
| Intubation/NIV, *N* (%) | 289 | 10 (9) | 15 (8) | 0.84 |
| ICU, *N* (%) | 288 | 14 (13) | 18 (10) | 0.47 |
| CAG, *N* (%) | 288 | 34 (31) | 63 (35) | 0.49 |
| Revascularization (PCI + CABG), *N* (%) | 97* | 19 (56) | 39 (62) | 0.31 |
| PCI, *N* (%) | 97* | 15 (44) | 35 (56) | 0.28 |
| CABG, *N* (%) | 97* | 4 (12) | 4 (7) | 0.35 |
| Left ventricular assist device, *N* (%) | 288 | 3 (3) | 0 (0) | 0.03 |
| Admission | | | | |
| Admission time, days (IQR) | 290 | 6 (4–12) | 4 (2–8) | < 0.001 |
| Discharged alive, *N* (%) | 290 | 101 (91) | 172 (96) | 0.072 |
| Readmission | | | | |
| Readmission (medical) < 1 month, *N* (%) | 290 | 29 (26) | 35 (20) | 0.19 |
| Readmission (medical) < 12 months, *N* (%) | 290 | 63 (57) | 77 (43) | 0.023 |
| Readmission due to HF < 1 month, *N* (%) | 290 | 16 (14) | 5 (3) | < 0.001 |
| Readmission due to HF < 12 months, *N* (%) | 290 | 34 (31) | 8 (5) | < 0.001 |

*Total number of CAGs

*CABG,* coronary artery bypass graft; *CAG,* coronary angiography; *ICU,* intensive care unit; *NIV,* non-invasive ventilation; *PCI,* percutaneous coronary intervention

**Table 4** Comparison of medication dispensed prior to admission and at discharge in patients with HFpEF and HFrEF in the DanAHF cohorte

| | *N* | At admission | | *P*-value | At discharge | | |
|---|---|---|---|---|---|---|---|
| | | HFrEF | HFpEF | | HFrEF | HFpEF | *P*-value |
| Diuretics, *N* (%) | 286 | 68 (63) | 77 (43) | 0.001 | 82 (77) | 91 (51) | < 0.001 |
| Beta blockers, *N* (%) | 284 | 62 (59) | 67 (38) | < 0.001 | 82 (77) | 102 (58) | 0.001 |
| Ace-inhibitors, *N* (%) | 286 | 34 (32) | 36 (20) | 0.03 | 46 (43) | 38 (22) | < 0.001 |
| Angiotensin receptor blockers, *N* (%) | 285 | 16 (15) | 23 (13) | 0.6 | 16 (15) | 24 (14) | 0.75 |
| Aldosterone antagonists, *N* (%) | 285 | 17 (16) | 9 (5) | 0.002 | 29 (27) | 17 (10) | < 0.001 |
| Anticoagulants, *N* (%) | 286 | 45 (42) | 66 (37) | 0.4 | 60 (57) | 86 (49) | 0.23 |
| Platelet inhibitors, *N* (%) | 286 | 30 (28) | 42 (24) | 0.4 | 44 (42) | 77 (44) | 0.73 |
| Calcium channel blockers, *N* (%) | 286 | 12 (11) | 31 (17) | 0.2 | 10 (9) | 29 (17) | 0.094 |
| Amiodarone, *N* (%) | 285 | 11 (10) | 1 (1) | < 0.001 | 12 (11) | 6 (3) | 0.009 |
| Digoxin, *N* (%) | 290 | 10 (9) | 16 (9) | 1 | 19 (18) | 18 (10) | 0.064 |
| COPD inhalors, *N* (%) | 286 | 19 (18) | 40 (23) | 0.3 | 19 (18) | 40 (23) | 0.33 |
| Antidepressants, *N* (%) | 286 | 11 (10) | 21 (12) | 0.7 | 11 (10) | 19 (11) | 0.90 |
| NSAIDS, *N* (%) | 286 | 0 (0) | 4 (2) | 0.1 | 1 (1) | 4 (2) | 0.41 |

*COPD,* chronic obstructive pulmonary disease; *NSAIDs,* non-steroidal anti-inflammatory drugs

10%, $p = 0.04$). No differences in the past medical history of diabetes, hypertension, stroke, or chronic kidney disease were seen.

Subdividing the 290 patients with acute HF and an available echocardiography into 3 groups instead of 2 results in the following: HFrEF (LVEF < 40%, $n = 93$), HFmrEF (LVEF 40–49%, $n = 43$), and HFpEF (≥ 50%, $n = 154$). Patients with HFpEF had a significantly shorter hospital admission compared to patients with HFmrEF and HFrEF (4 days vs. 7 and 6 days, $p < 0.001$). There was no significant difference in medical readmission due to any cause within 1 month or 1 year between the groups. There was a significant difference between the groups comparing readmission rate due to HF both within 1 month (HFpEF 2%, HFmrEF 9%, and HFrEF

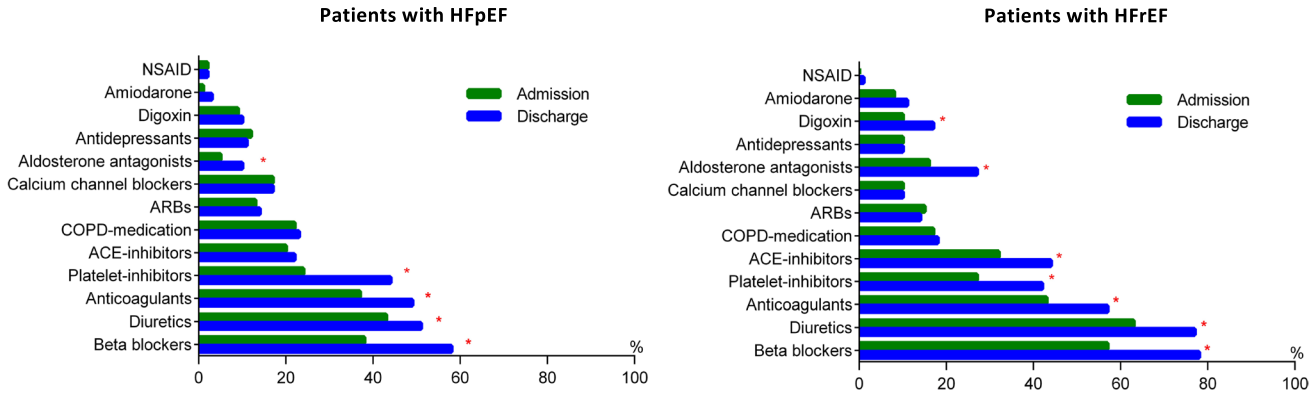


**Fig. 2** Comparison of medication dispensed prior to admission and at discharge for patients with HFpEF and HFrEF respectively. *Statistically significant changes. ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs

15%, $p < 0.001$) and within 1 year (HFpEF 4%, HFmrEF 14%, and HFrEF 32%, $p < 0.001$).

## Discussion

The current nationwide DanAHF study provides a large set of data including all medical admissions in Denmark for an entire week, with more than 5000 patient admissions. A total of 335 was according to predefined symptom and treatment algorithm categorized as acute HF patients. This enables an analysis of a consecutive and unselected cohort of acute HF patients and facilitates an understanding of this complex population in order to optimize future studies in the field. In the DanAHF population, only 32% of the patient had a past medical history of HF meaning that 68% had de novo HF. With a LVEF limit of 45%, a total of 62% of the acute HF patients were diagnosed with HFpEF and 38% with HFrEF, confirming previous large observational studies showing that patients with HFpEF are a frequent cause of acute HF [18–20]. Compared to patients with HFrEF, patients with HFpEF had a shorter admission period and a lower rate of readmissions due to HF. Furthermore, there was a nonsignificant tendency towards more patients with HFpEF being discharged alive. Patients with HFpEF were less likely to have a past medical history with IHD, congestive HF, and an implanted pacemaker/ICD, indicating a more favorable pre-admission cardiac status compared to patients with HFrEF. The lower cardiac comorbidity burden may be a reason for the significantly shorter hospital stay for patients with HFpEF.

Most HFpEF studies to date found patients with HFpEF to be older with a higher prevalence of hypertension and atrial fibrillation compared to patients with HFrEF [3, 21]. In the DanAHF population, no significant difference in these parameters was seen. It is well known that comorbidity increases with age, indicating why patients with HFpEF and HFrEF of similar age in the DanAHF population also have the same prevalence of hypertension and atrial fibrillation. Furthermore, a mean age of 71 years among patients with HFpEF in the DanAHF study is similar to the mean age in the meta-analysis MAGGIC [21]. This possibly suggests that the same comorbidity prevalence among patients with HFpEF and HFrEF is more likely due to a higher mean age among patients with HFrEF in the DanAHF population than to a phenotypical different HFpEF population.

The pathophysiology in HFpEF is defined as an abnormal active relaxation of the left ventricle along with increased passive chamber stiffness. As a direct consequence, the patients will exhibit a disproportionate increase in left ventricle filling pressure with an increase in volume or afterload and thus vulnerable to develop pulmonary oedema [22]. Consistent with a higher systolic blood pressure among patients with HFpEF in the DanAHF study. Except for the EMPEROR-Preserved Trial finding a lower incidence of hospitalization for HF among patients with HFpEF treated with empagliflozin [10], no treatment has to date significantly shown to reduce morbidity or mortality. Current treatment options therefore focus on symptoms and comorbidity [9]. It has been suggested that treating especially systolic hypertension plays an important role in patients with HFpEF, and that diuretics improve symptoms of HF irrespective of LVEF [9]. In the current study, it is accordingly seen that diuretics and antihypertensive medication are prevalent among patients with HFpEF.

## Clinical Presentation

At hospital admission, patients with HFpEF presented with a significantly higher systolic blood pressure and a lower heart rate compared to patients with HFrEF, indicating two hypotheses: (1) hypertensive pulmonary edema was more common among patients with HFpEF, supported by the higher proportion of patients with HFpEF receiving nitroglycerine, despite no difference in the number of CAGs performed. (2) Patients with HFrEF had a lower stroke volume, especially when decompensated, supported by the fact that significantly more patients with HFrEF received inotropes during admission. Fewer patients with HFpEF were treated with IV diuretics and were also less likely to have X-ray-verified stasis or cardiomegaly, suggesting less congestion in patients with HFpEF.

It is well known that patients with HFrEF often have abnormal ECGs; this study reveals that it does not apply to patients with HFpEF to the same degree. CAGs were only performed in one-third of the acute HF patients with approximately 60% of them receiving revascularization. This accentuating that the DanAHF population not only included patients with myocardial infarction but also reflects a real-world HF population.

## Mortality

Comparing mortality rates in patients with HFpEF and HFrEF, the literature is not consistent. Epidemiological and registry-based studies have reported similar survival in the two groups, but later, a meta-analysis from 2009 demonstrated that mortality in patients with HFpEF was only half the mortality observed in patients with HFrEF [6, 18, 23, 24]. This was later supported in the "Meta-analysis Global Group in Chronic Heart Failure" (MAGGIC) from 2012 including 31 studies and nearly 42,000 patients, showing that patients with HFrEF have a higher risk of death than patients with HFpEF [21]. However, the MAGGIC study also illustrated that initial mortality between HFrEF and HFpEF is comparable, consistent with a non-significant difference in survival to discharge in the current study of the DanAHF population.

## Limitations

As any other retrospective study, the DanAHF study is exposed to limitations inherent in observational studies. Inclusion criteria were created with the purpose of identifying a true and unselected population of patients with acute HF, unlike many other studies performed up till now. The diagnosis of HF was established by a review of hospital records, ensuring relevant signs, symptoms, and treatment. However, we cannot out rule that patients with acute HF may have been missed due to a lack of documented information.

ESC Guidelines from 2016 subdivide HF in HFrEF (LVEF < 40%), HFmrEF (LVEF 40–49%), and HFpEF (≥ 50%) [9]. All subgroups should by definition have symptoms of HF that may be accompanied by signs. To fulfil the diagnostic criteria for HFmrEF and HFpEF, natriuretic peptides should be elevated, and/or echocardiographic signs of HF should be present (relevant structural heart disease or diastolic dysfunction). Shortage in these last criteria in the DanAHF study could result in a deficient diagnosis. Furthermore, a potential diversity in echocardiographic measurements could lead to intercenter and interindividual bias.

Of the population with acute HF, 13% had no available echocardiography and could not be included for further analysis. The difference in cardiac comorbidity between the group with a missing echocardiography and the patients with HFpEF/HFrEF could explain why some patients did not have an echocardiography performed. Due to the fact that in a clinical setting, the probability of having an echocardiography performed increases with cardiac comorbidity. Another explanation could be that clinicians due to a history of COPD interpreted symptoms as COPD exacerbations instead of HF and therefore did not perform an echocardiography. Furthermore, an advanced cancer diagnosis could have made an echocardiography inconsequential.

# Conclusion

Of acute HF admissions, nearly two-thirds were due to HFpEF. Patients with HFpEF were less likely to have a past medical history with IHD, congestive HF and an implanted pacemaker/ICD, indicating a more favorable pre-admission cardiac status compared to patients with HFrEF. Patients with HFpEF were during admission less frequently treated with IV diuretics and inotropes, indicating a higher stroke volume and less congestion compared to patients with HFrEF. There was no significant difference in the use of intubation/NIV, ICU admissions, or revascularization. Patients with HFpEF had a 2-day shorter admission period, but there was no significant difference in survival to discharge in the two groups. By describing the characteristics of the HFpEF phenotype, this article hopefully both contributes to a clinical awareness of these patients and improves future planning of HFpEF studies in order to develop successful treatment modalities and options.

**Abbreviations** *ACEI*: ACE-inhibitor; *ARB*: Angiotensin receptor blockers; *BMI*: Body mass index; *CABG*: Coronary artery bypass graft; *CAG*: Coronary angiography; *COPD*: Chronic obstructive pulmonary disease; *HF*: Heart failure; *HFpEF*: Heart failure with preserved ejection fraction; *HFrEF*: Heart failure with reduced ejection fraction;

*ICD*: Implantable cardioverter defibrillator; *ICU*: Intensive care unit; *IHD*: Ischemic heart disease; *LVEF*: Left ventricular ejection fraction; *MRA*: Aldosterone antagonists; *NIV*: Non-invasive ventilation; *PCI*: Percutaneous coronary intervention

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**Author Contribution** ML interpreted the data and drafted the work. ES analyzed the data and revised the work. HS was a major contributor in writing the manuscript. CH and JM substantively revised the work. NK and MGL designed and revised the work. All authors read and approved the final manuscript.

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**Data Availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics Approval and Consent to Participate** The DanAHF study and data collection has been authorized by the Danish Health and Medicines Authorities.

**Consent for Publication** Not applicable.

**Competing Interests** The authors declare no competing interests.

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