ORIGINAL RESEARCH ARTICLE

Is heart failure misdiagnosed in hospitalized patients with preserved ejection fraction? From the European Society of Cardiology - Heart Failure Association EURObservational Research Programme Heart Failure Long-Term Registry

Agnieszka Kapłon-Cieślicka[1]*, Cécile Laroche[2], Maria G. Crespo-Leiro[3], Andrew J.S. Coats[4], Stefan D. Anker[5], Gerasimos Filippatos[6], Aldo P. Maggioni[2,7], Camilla Hage[8], Antonio Lara-Padrón[9], Alessandro Fucili[10], Jarosław Drożdż[11], Petar Seferovic[12], Giuseppe M.C. Rosano[4], Alexandre Mebazaa[13], Theresa McDonagh[14], Mitja Lainscak[15], Frank Ruschitzka[16], Lars H. Lund[8] and on behalf of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) and the ESC Heart Failure Long-Term Registry Investigators[†]

[1]*1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland;* [2]*EURObservational Research Programme (EORP), European Society of Cardiology, Sophia-Antipolis, France;* [3]*Unidad de Insuficiencia Cardiaca y Trasplante Cardiaco, Complexo Hospitalario Universitario A Coruna (CHUAC), INIBIC, UDC, CIBERCV, A Coruña, Spain;* [4]*IRCCS San Raffaele, Pisana, Rome, Italy;* [5]*Division of Cardiology and Metabolism; Department of Cardiology (CVK); and Berlin-Brandenburg Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany & Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Göttingen, Germany;* [6]*School of Medicine, University of Cyprus & Heart Failure Unit, Department of Cardiology, University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece;* [7]*ANMCO Research Centre, Florence, Italy;* [8]*Unit of Cardiology, Department of Medicine, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden;* [9]*Unidad de Insuficiencia Cardiaca, Servicio de Cardiología, Complejo Hospital Universitario de Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife, Spain;* [10]*Department of Medical Sciences, University of Ferrara, Ferrara, Italy;* [11]*Department of Cardiology, Medical University of Lodz, Lodz, Poland;* [12]*Faculty of Medicine, University of Belgrade; Serbian Academy of Sciences and Arts, Belgrade, Serbia;* [13]*Department of Anaesthesia and Critical Care, University Hospitals Saint Louis-Lariboisière, APHP; University Paris Diderot; UMR 942 Inserm – MASCOT, Paris, France;* [14]*King's College Hospital, London, UK;* [15]*Department of Internal Medicine, General Hospital Murska Sobota, Slovenia, and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia;* [16]*Clinic of Cardiology, University Hospital, Zürich, Switzerland*

Abstract

Aims   In hospitalized patients with a clinical diagnosis of acute heart failure (HF) with preserved ejection fraction (HFpEF), the aims of this study were (i) to assess the proportion meeting the 2016 European Society of Cardiology (ESC) HFpEF criteria and (ii) to compare patients with restrictive/pseudonormal mitral inflow pattern (MIP) vs. patients with MIP other than restrictive/pseudonormal.

Methods and results   We included hospitalized participants of the ESC-Heart Failure Association (HFA) EURObservational Research Programme (EORP) HF Long-Term Registry who had echocardiogram with ejection fraction (EF) $\geq 50\%$ during index hospitalization. As no data on e', E/e' and left ventricular (LV) mass index were gathered in the registry, the 2016 ESC HFpEF definition was modified as follows: elevated B-type natriuretic peptide (BNP) (≥ 100 pg/mL for acute HF) and/or N-terminal pro-BNP (≥ 300 pg/mL) and at least one of the echocardiographic criteria: (i) presence of LV hypertrophy (yes/no), (ii) left atrial volume index (LAVI) of >34 mL/m^2), or (iii) restrictive/pseudonormal MIP. Next, all patients were divided into four groups: (i) patients with restrictive/pseudonormal MIP on echocardiography [i.e. with presumably elevated left atrial (LA) pressure], (ii) patients with MIP other than restrictive/pseudonormal (i.e. with presumably normal LA pressure), (iii) atrial fibrillation (AF) group, and (iv) 'grey area' (no consistent description of MIP despite no report of AF). Of 6365 hospitalized patients, 1848 (29%) had EF $\geq 50\%$. Natriuretic peptides were assessed in 28%, LV hypertrophy in 92%, LAVI in 13%, and MIP in 67%. The 2016 ESC HFpEF criteria could be assessed in 27% of the 1848 patients and, if assessed, were met in 52%. Of the 1848 patients, 19% had restrictive/pseudonormal MIP, 43% had MIP other than restrictive/pseudonormal, 18% had AF and 20% were grey area. There were no differences in long-term all-cause or cardiovascular mortality, or all-cause hospitalizations or HF rehospitalizations between the four groups. Despite fewer non-cardiac comorbidities reported at baseline, patients with MIP other than restrictive/pseudonormal (i.e. with presumably normal LA pressure) had more non-cardiovascular (14.0 vs.

6.7 per 100 patient-years, *P* < 0.001) and cardiovascular non-HF (13.2 vs. 8.0 per 100 patient-years, *P* = 0.016) hospitalizations in long-term follow-up than patients with restrictive/pseudonormal MIP.

Conclusions   Acute HFpEF diagnosis could be assessed (based on the 2016 ESC criteria) in only a quarter of patients and confirmed in half of these. When assessed, only one in three patients had restrictive/pseudonormal MIP suggestive of elevated LA pressure. Patients with MIP other than restrictive/pseudonormal (suggestive of normal LA pressure) could have been misdiagnosed with acute HFpEF or had echocardiography performed after normalization of LA pressure. They were more often hospitalized for non-HF reasons during follow-up. Symptoms suggestive of acute HFpEF may in some patients represent non-HF comorbidities.

Introduction

Compared with heart failure (HF) with reduced ejection fraction (HFrEF), the diagnosis of HF with preserved EF (HFpEF) remains challenging.[1–4] HFpEF is accompanied by multiple cardiovascular and non-cardiovascular comorbidities, potentially confusing the HFpEF diagnosis, as some of them present with symptoms that can mimic HF.[5–9] A growing understanding of the pathophysiology and clinical characteristics of HFpEF has resulted in proposals to identify a distinct clinical entity and attempts to develop specific diagnostic criteria.[1–4] Among these is the 2016 European Society of Cardiology (ESC) definition.[1]

In the ESC EURObservational Research Programme (EORP) HF Long-Term (LT) Registry, EF of >45% was significantly more often reported in hospitalized compared with ambulatory HF patients (33% vs. 23%), suggesting that the diagnosis of HFpEF is more readily made in the acute setting.[10] A definite diagnosis of HFpEF requires echocardiographic assessment of diastolic dysfunction and left atrial (LA) pressure, which may frequently be neglected in clinical practice.[4,11] Mitral inflow patterns (MIPs) other than restrictive or pseudonormal indicate normal LA pressures and thus preclude left ventricular (LV) dysfunction as a leading cause of symptoms in acutely ill patients.[4,12–15]

We hypothesized that, in clinical practice, a substantial proportion of hospitalized patients with an EF of ≥50% and acute symptoms suggestive of HF do not have echocardiographic signs of increased LA pressure and thus, might be potentially misdiagnosed as having acute HFpEF. These patients might be burdened with comorbidities which may, at least in part, account for their clinical presentation and outcomes.

The aim was to assess the prevalence of HFpEF in hospitalized ESC-HF LT Registry participants with an EF of ≥50%, based on (i) the 2016 ESC diagnostic criteria and (ii) echocardiographic signs of elevated LA pressure, defined as restrictive or pseudonormal MIP. Next, we sought to investigate differences in baseline characteristics and long-term prognosis of patients with and without restrictive/pseudonormal MIP.

Methods

Material and patient selection

The ESC HF LT Registry was a prospective, multicentre, observational study of HF patients, conducted by the EORP in 337 cardiology centres from 33 ESC Member countries (Supporting Information, *Appendix S1*). The registry included adult HF patients (aged 18 years or more), both those hospitalized for acute HF and ambulatory patients with chronic HF. There were no specific exclusion criteria. Data on subsequent hospital admissions and mortality were obtained at a mandatory follow-up visit at 12 months (if the patient was unable to reach the clinical centre, the follow-up visit was replaced by a telephone call). The registry was approved by local ethical review boards according to the regulations of each participating country. All patients enrolled in the survey signed an informed consent, unless exempt by the local ethics committee.[16,17]

The current analysis included patients hospitalized for acute HF who had an echocardiogram with EF ≥ 50% during the index hospitalization. Patients with acute HFrEF (EF < 40% on echocardiogram performed during the index hospitalization) and HF with mid-range EF (HFmrEF; EF 40–49%) were included for outcome comparisons only.

Assessment of the 2016 European Society of Cardiology criteria for heart failure with preserved ejection fraction

We first assessed if the 2016 ESC criteria for HFpEF[1] were met: elevated concentrations of natriuretic peptides [for acute HF: B-type natriuretic peptide (BNP) of ≥100 pg/mL and/or N-terminal pro-BNP (NT-proBNP) of ≥300 pg/mL]

and at least one of the echocardiographic criteria: (i) presence of LV hypertrophy (yes/no; no data on LV mass index were collected in the registry), (ii) LA enlargement [left atrial volume index (LAVI) of >34 mL/m^2], or (iii) diastolic dysfunction [as no tissue Doppler imaging (TDI)-derived data (including e' and E/e' ratio) were gathered in the registry, we used a surrogate in the form of restrictive or pseudonormal MIP].

Comparison of patients with and without restrictive/pseudonormal mitral inflow pattern

Next, we sought to identify and compare patients with restrictive/pseudonormal MIP suggestive of elevated LA pressure and patients with MIP other than restrictive/pseudonormal who might have had normal LA pressures despite having been diagnosed with acute HFpEF. Given the lack of some data in the registry [including e', E/e' ratio, and tricuspid regurgitation velocity (TRV) unavailable in all patients, LAVI missing in 87%], we were unable to accurately follow the algorithm for LA pressure estimation proposed by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[4] Natriuretic peptides concentrations were missing in 72% of patients. Thus, we divided patients into four groups based on MIP on echocardiography performed during index hospitalization:

1 patients with restrictive/pseudonormal MIP suggestive of elevated LA pressure (*Table 1*),
2 patients with MIP other than restrictive/pseudonormal, suggestive of normal LA pressure (*Table 1*),
3 'atrial fibrillation (AF) group'—patients who most likely had AF during echocardiographic evaluation, which made it impossible to assess MIP (this included patients with AF in electrocardiograms performed during index hospitalization and with no data on MIP on echocardiography),
4 'grey area'—patients with MIP assessed but impossible to classify (as defined in *Table 1*) or with no data on MIP despite no report of AF during index hospitalization.

We compared these four groups with regard to baseline characteristics, course of index hospitalization (clinical status, laboratory tests' results, and implemented therapies), and in-hospital and long-term outcomes.

For completeness, we also compared long-term prognosis (all-cause death and all-cause death or HF rehospitalization) of patients with EF $\geq$ 50% and restrictive/pseudonormal MIP and patients with EF $\geq$ 50% and MIP other than restrictive/pseudonormal with that of HFrEF and of HFmrEF patients but performed no other analyses on HFrEF or HFmrEF. The hypothesis behind that analysis was that patients with EF $\geq$ 50% and restrictive/pseudonormal MIP might have prognosis more similar to that of 'true' HF (i.e. HFrEF or HFmrEF), while patients with EF $\geq$ 50% and MIP other than restrictive/pseudonormal might be at a lower risk of death and HF events.

Statistical analysis

Categorical data were presented as percentages. Continuous variables were reported as median and interquartile range or as mean ± standard deviation as appropriate. For categorical variables, among-group comparisons were made using a χ^2 test or a Fisher's exact test. For continuous variables, among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Long-term outcomes were presented as event rates per 100 patient-years, and pairwise comparisons between groups were made using Poisson regression model. Kaplan–Meier curves were plotted for all-cause death and a composite of all-cause death and HF rehospitalization and pairwise comparisons were performed between the groups. All tests were two-sided. For all tests, a *P* value of less than 0.05 was deemed significant. All statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Table 1 Echocardiographic estimation of left atrial (LA) pressure based on mitral inflow pattern and data available in the ESC-HFA EORP Heart Failure Long-Term Registry

Estimated LA pressure	Mitral inflow pattern	Data in the registry[a]
Presumably elevated	restrictive or pseudonormal	• mitral inflow pattern described as restrictive/pseudonormal (and E/A > 0.8, if E/A ratio available), • or E/A ≥ 2 (if only E/A ratio given)
Presumably normal	other than restrictive/pseudonormal (normal or impaired relaxation)	• mitral inflow pattern described as other than restrictive/pseudonormal (and E/A < 2, if E/A ratio available), • or E/A ≤ 0.8 (if only E/A ratio given)
Impossible to classify[b]	impossible to classify or not assessed	• no description of mitral inflow pattern and no data on E/A ratio, • or E/A between 0.8 and 2.0 (if only E/A ratio given) • both description of mitral inflow pattern and E/A ratio given, but their results - inconsistent

ESC, European Society of Cardiology; EORP, EURObservational Research Programme; HFA, Heart Failure Association.
[a]In the registry, data on mitral inflow pattern were entered: (i) dichotomously as 'restrictive/pseudonormal pattern'—yes vs. no, (ii) as E/A ratio.
[b]Included in the 'grey area' group if no atrial fibrillation present.

Results

Patients

A total of 19 135 patients were enrolled in the registry between March 2011 and May 2017, including 6365 hospitalized patients with EF assessed echocardiographically during the index hospitalization. Out of these, 1848 patients (29%) had an EF of ≥50%—these patients were included in further analyses (flow-chart, *Figure 1*).

Prevalence of heart failure with preserved ejection fraction based on the 2016 European Society of Cardiology criteria

In 1848 patients with EF ≥50%, we displayed the extent to which individual criteria were assessed, and if they were assessed, to what extent criteria for HFpEF were met (*Figure 2A*), and the extent to which it was possible to assess the 2016 ESC HFpEF definition (in 27%), and if assessed, to what extent the 2016 ESC HFpEF definition was met (in 52% of the 27% possible to assess) (*Figure 2B*).

Patient groups based on mitral inflow pattern

Out of 1848 patients, 19% had restrictive/pseudonormal MIP indicative of elevated resting LA pressure, while 43% had MIP other than restrictive/pseudonormal suggestive of normal LA pressure (*Figure 1*). Clinical, laboratory, and echocardiographic characteristics of the four groups (patients with restrictive/pseudonormal MIP, patients with MIP other than restrictive/pseudonormal, AF group and grey area patients) are presented in *Table 2*.

Outcomes of patients with and without restrictive/pseudonormal mitral inflow patterns

Median follow-up was 393 days (interquartile range: 366–539 days). In-hospital and long-term outcomes of the four groups are presented in *Tables 3* and *4*, and in *Figure 3*. There were no significant differences between the four groups with regard to in-hospital mortality, long-term all-cause and cardiovascular mortality, as well as long-term all-cause hospitalizations. However, notably, patients with MIP other than restrictive/pseudonormal had a rate of non-cardiovascular hospitalizations twice as high as patients with restrictive/pseudonormal MIP. Furthermore, patients with MIP other than restrictive/pseudonormal also had a significantly higher rate of cardiovascular non-HF hospitalizations in long-term follow-up than patients with restrictive/pseudonormal MIP.

Kaplan–Meier curves for comparison of long-term outcomes of patients with EF ≥ 50% and restrictive/pseudonormal MIP, patients with EF ≥ 50% and MIP other than restrictive/pseudonormal, HFmrEF and HFrEF are shown in *Figure 4*. Pairwise comparisons of all-cause mortality showed significantly lower survival ($P < 0.001$) in HFrEF compared with all three remaining groups, with no statistically significant differences between the three remaining groups.

Figure 1 Patient selection and distribution between groups. AF, atrial fibrillation; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MIP, mitral inflow pattern; pts, patients; TTE, transthoracic echocardiogram.
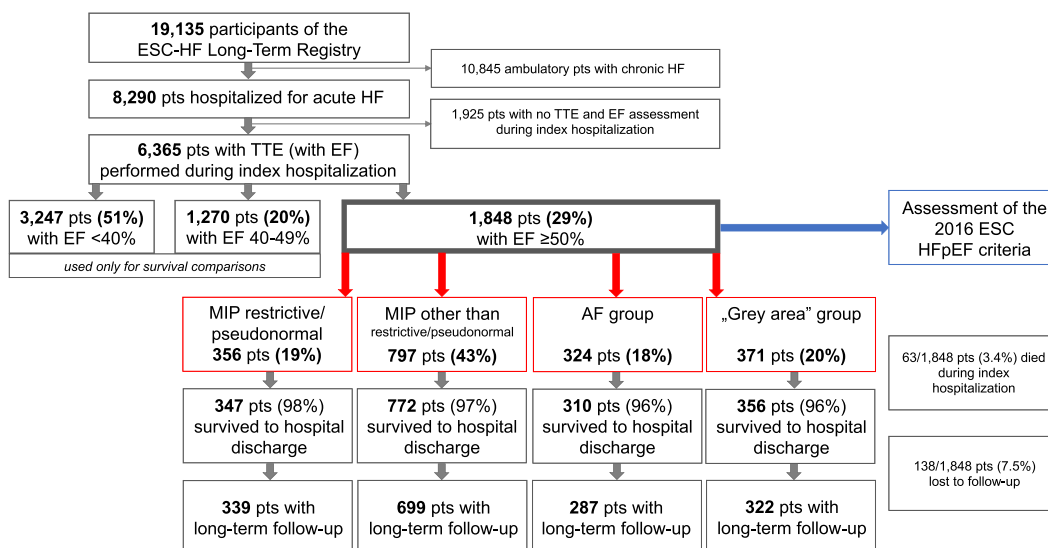
Figure 2 Proportion of patients meeting the 2016 ESC criteria for heart failure with preserved ejection fraction: (A) patients meeting individual criteria, (B) patients meeting the 2016 ESC definition. BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; NTproBNP, N-terminal proBNP; pts, patients.
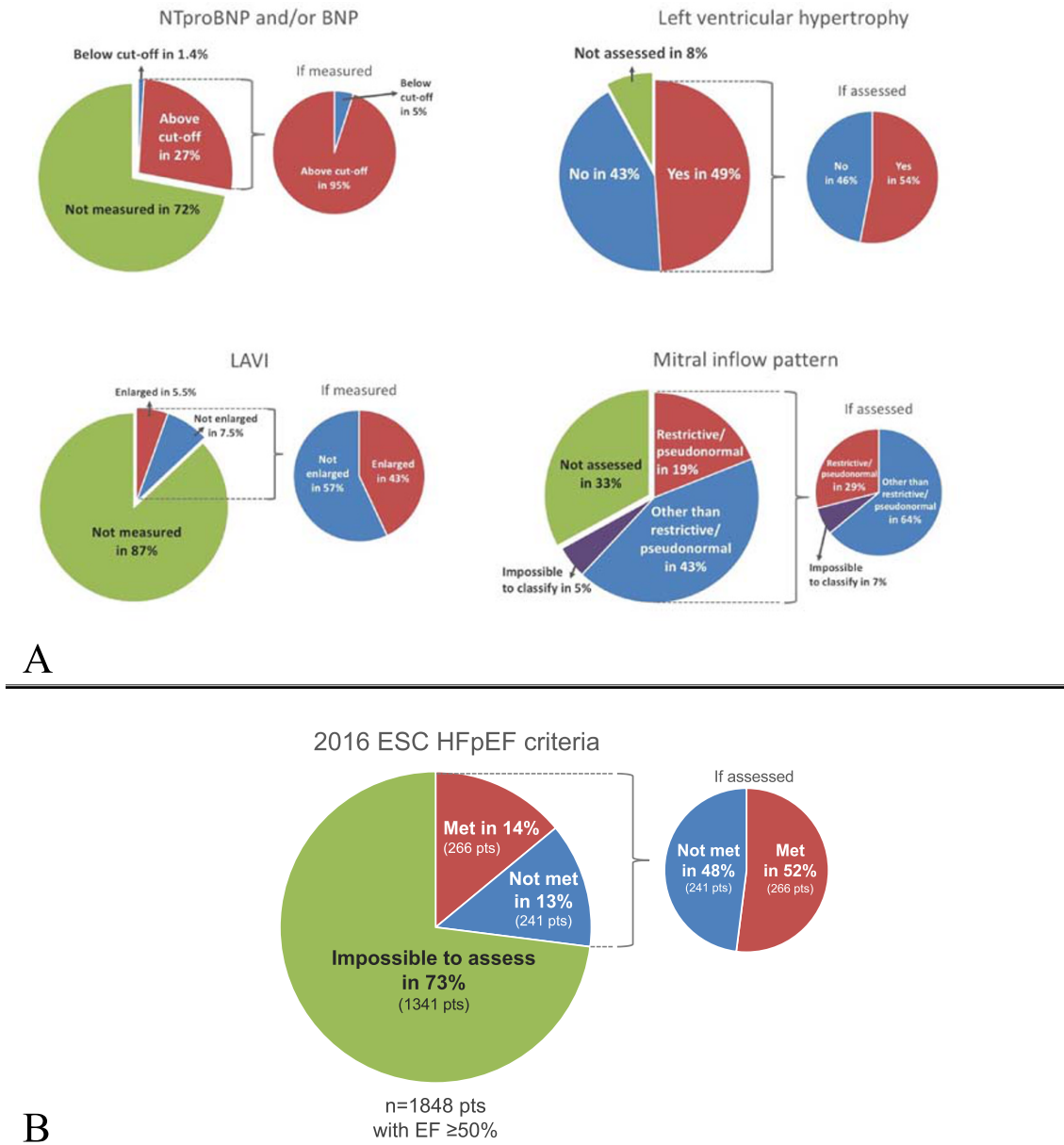
For the composite of all-cause death or rehospitalization for HF, pairwise comparisons showed again significantly worse outcomes ($P < 0.001$) in HFrEF vs. all three remaining groups, as well as in patients with HFpEF and restrictive/pseudonormal MIP compared with the HFmrEF group ($P = 0.01$). There was a trend towards greater risk for patients with HFpEF and restrictive/pseudonormal MIP vs. patients with EF $\geq$ 50% and MIP other than restrictive/pseudonormal ($P = 0.08$). There was no significant difference between the HFmrEF group and patients with EF $\geq$ 50% and MIP other than restrictive/pseudonormal.

Thus, in summary, among patients diagnosed with acute HFpEF (EF $\geq$ 50%), those with restrictive/pseudonormal MIP (suggestive of elevated LA pressure) vs. those with MIP other than restrictive/pseudonormal (i.e. with presumably normal LA pressure) had lower risk of non-cardiovascular and cardiovascular non-HF hospitalizations, and a trend towards higher risk of death or HF rehospitalization in long-term follow-up.

Table 2 Baseline characteristics of the four groups of patients with preserved ejection fraction

Variable	Hospitalized patients with EF ≥ 50% (n = 1848)				
	MIP restrictive/pseudonormal (n = 356)	MIP other than restrictive/pseudonormal (n = 797)	AF group (n = 324)	Grey area group (n = 371)	P^a
Clinical characteristics prior to index hospitalization					
Age (years)	72 (62–80)	74 (64–81)	76 (66–83)	73 (63–81)	**<0.001**
Female gender	55%	56%	59%	49%	0.06
BMI (kg/m²)	29 (26–35)	28 (25–31)	27 (24–31)	27 (25–31)	**<0.001**
Obesity (BMI ≥30 kg/m²)	45%	34%	33%	32%	**0.001**
HF diagnosis >12 months	26%	29%	38%	28%	**0.008**
Previous HF hospitalization	30%	28%	34%	28%	0.20
Last known EF (i.e. before index hospitalization)	67% n = 238	62% n = 491	62% n = 175	61% n = 213	0.33
Hypertension	79%	76%	69%	68%	**<0.001**
CAD/previous MI	52%	42%	31%	51%	**<0.001**
Prior stroke or TIA	22%	13%	17%	15%	**0.001**
History of AF	48%	46%	95%	34%	**<0.001**
Peripheral vascular disease	24%	15%	16%	17%	**0.004**
History of VTE	15%	4.2%	6.0%	6.9%	**<0.001**
Diabetes	38%	36%	31%	34%	0.22
Chronic kidney disease	29%	27%	22%	21%	**0.03**
COPD	35%	21%	20%	25%	**<0.001**
Sleep apnoea	4.0%	4.7%	4.0%	2.3%	0.33
Hepatic dysfunction	12%	6.0%	7.7%	4.0%	**<0.001**
Thyroid dysfunction	12%	9.6%	16%	8.8%	**0.03**
Current malignant disease	5.6%	6.6%	6.2%	4.3%	0.46
Depression	17%	9.5%	7.1%	9.2%	**<0.001**
Number of non-cardiac co-morbidities[b]	2.7 (±2.1)	2.0 (±1.7)	1.9 (±1.5)	1.8 (±1.5)	**<0.001**
Three or more non-cardiac co-morbidities[b]	45%	32%	32%	28%	**<0.001**
Smoking	16%	12%	9.9%	13%	0.09
Clinical presentation at hospital admission					
Heart rate (b.p.m.)	90 (72–112)	80 (70–100)	90 (74–120)	80 (70–100)	**<0.001**
AF at hospital admission	30%	34%	100%	4.6%	**<0.001**
SBP (mm Hg)	145 (121–170)	140 (120–160)	130 (120–150)	140 (120–160)	**<0.001**
NYHA class:					**<0.001**
NYHA II	15%	25%	8.5%	19%	
NYHA III	50%	48%	58%	53%	
NYHA IV	35%	27%	34%	28%	
Pulmonary rales	84%	72%	74%	69%	**<0.001**
Pulmonary congestion/alveolar oedema on chest X-ray	81%	64%	66%	59%	**<0.001**
Peripheral oedema	50%	47%	68%	46%	**<0.001**
Uncontrolled hypertension as a cause of admission	44%	26%	22%	25%	**<0.001**
Laboratory findings on admission					
NT-proBNP (pg/mL)	3818 (1842–7419) n = 48	2611 (1133–5482) n = 203	3510 (1848–5650) n = 62	2781 (1372–6056) n = 62	0.16
BNP (pg/mL)	424 (229–1224) n = 16	426 (182–679) n = 73	489 (253–879) n = 34	444 (193–826) n = 41	0.67
Serum creatinine (mg/dL)	1.1 (0.9–1.4) n = 356	1.1 (0.9–1.4) n = 789	1.1 (0.9–1.3) n = 282	1.1 (0.9–1.4) n = 338	0.08
Urea (mg/dL)	29 (19–44) n = 305	32 (20–49) n = 641	31 (23–51) n = 215	28 (19–45) n = 279	**0.04**

(Continues)

Table 2 (continued)

Variable	Hospitalized patients with EF ≥ 50% (n = 1848)		AF group (n = 324)	Grey area group (n = 371)	P^a
	MIP restrictive/pseudonormal (n = 356)	MIP other than restrictive/pseudonormal (n = 797)			
Sodium (mmol/L)	139 (136–142) n = 338	139 (136–141) n = 782	139 (136–142) n = 269	139 (136–141) n = 332	0.30
Haemoglobin (g/dL)	12 (11–14) n = 354	13 (11–14) n = 789	12 (11–14) n = 279	13 (11–14) n = 339	0.16
Echocardiography during index hospitalization					
EF (%)	60 (54–65)	58 (54–62)	55 (52–60)	56 (53–60)	<0.001
LVEDD (mm)	55 (49–57) n = 334	50 (45–56) n = 735	51 (45–56) n = 236	50 (46–57) n = 281	<0.001
Left ventricular hypertrophy	74% n = 355	45% n = 788	48% n = 255	55% n = 310	<0.001
LAVI (mL/m²)	37 (28–49) n = 46	28 (22–40) n = 141	47 (30–72) n = 33	28 (23–65) n = 26	<0.001
Left atrial dimension (mm)	45 (39–51) n = 176	44 (40–50) n = 329	51 (46–56) n = 90	44 (38–50) n = 110	<0.001
Aortic stenosis moderate–severe	21% n = 356	14% n = 797	13% n = 261	22% n = 321	<0.001
Aortic regurgitation moderate–severe	9.8% n = 356	13% n = 797	14% n = 259	14% n = 321	0.28
Mitral regurgitation moderate–severe	43% n = 356	34% n = 797	48% n = 262	36% n = 322	<0.001
Tricuspid regurgitation moderate–severe	33% n = 355	27% n = 797	52% n = 261	26% n = 319	<0.001

AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischemic attack; VTE, venous thromboembolism.
[a]P - for comparison between the four groups.
[b]Non-cardiac co-morbidities include: prior stroke or TIA, peripheral vascular disease, history of VTE, diabetes, chronic kidney disease, COPD, sleep apnoea, hepatic dysfunction, history of thyroid dysfunction, current malignant disease, depression, rheumatoid arthritis, Parkinson, anaemia (Hgb < 13 g/dL for men and <12 g/dL for women).
Bolded font indicates p values of <0.05.

Discussion

In this large generalizable study of acute presumed HFpEF (EF ≥ 50%), a diagnosis of HFpEF based on the 2016 ESC HF guidelines could be assessed in only a quarter of patients, and was confirmed in only half of these. Patients with HFpEF and signs of elevated LA pressure on echocardiography had lower risk of subsequent non-HF hospitalizations, and potentially greater risk of death or HF rehospitalization.

Several different HFpEF definitions have been proposed, from a symptom-based, in part 'diagnosis of exclusion' approach in early randomized clinical trials, to biomarker-orientated and echocardiography-orientated diagnostic criteria in recent trials and guidelines.[1–4,18–23] The latter put particular emphasis on the presence of objective evidence of structural and/or functional disease. The most recent Heart Failure Association (HFA)-Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final aetiology (PEFF) score includes a number of variables (grouped within the functional, morphological, and biomarker domain) to be assessed when diagnosing HFpEF.[3] Although natriuretic peptides carry undeniable importance in the diagnostic and prognostic evaluation of HF, their specificity may be limited in elderly patients with multiple comorbidities (such as AF, renal failure, frailty/cachexia, or respiratory diseases)—which represents a common clinical setting in HFpEF.[7] The 2016 guideline-recommended upper limits of natriuretic peptides' concentrations constitute exclusionary cut-off points, and should be used for ruling-out, rather than ruling in, a HF diagnosis.[1] The HFA-PEFF score, on the other hand, introduced different cut-offs for natriuretic peptides, depending on the presence or absence of AF (with cut-points in AF three times higher than in sinus rhythm), as well as on criterion type (major vs minor).[3] Importantly, the HFA-PEFF score is dedicated for diagnosing chronic HFpEF.[3] In our study, natriuretic peptides were elevated in all four analysed groups (i.e. HF could not be 'ruled out'), with the highest NT-proBNP concentrations in patients with restrictive/pseudonormal MIP and the 'AF group'. Increased natriuretic peptides in patients with MIP other than restrictive/pseudonormal (suggestive of normal LA pressure) and the grey area group might be explained primarily by the fact that they were measured at presentation whereas echocardiography may have been delayed allowing clinical improvement, or by old age, presence of chronic kidney disease in approximately one quarter, chronic obstructive pulmonary disease in one fifth and uncontrolled hypertension in one quarter of those patients, and presence of AF at hospital admission in one third of patients with MIP subsequently described as other than restrictive/pseudonormal.

Pulmonary congestion is secondary to an increase in LV filling pressures, and thus, in a decompensated HF patient, at least with acute dyspnoea, evidence for elevated LA

Table 3 Clinical course of index hospitalization, implemented therapies and in-hospital outcomes of the four groups of patients with preserved ejection fraction

Variable	MIP restrictive/ pseudonormal $n = 356$	MIP other than restrictive/ pseudonormal $n = 797$	AF group $n = 324$	Grey area group $n = 371$	P^a
In-hospital management and outcomes					
Nitrates during hospitalization	43%	27%	19%	24%	**<0.001**
Diuretics during hospitalization	83%	82%	81%	72%	**<0.001**
Coronary angiography during hospitalization	17%	19%	11%	23%	**<0.001**
PCI/CABG during hospitalization	7.0%	9.4%	2.8%	9.0%	**0.003**
Hospitalization length (days)	7 (4–12)	7 (5–11)	7 (5–12)	7 (4–13)	0.74
Death during hospitalization	2.5% 9/356	3.1% 25/797	4.3% 14/324	4.0% 15/371	0.51
Clinical status at discharge[b]					
Heart rate (b.p.m.)	68 (60–75)	70 (63–80)	74 (66–85)	70 (64–78)	**<0.001**
SBP (mm Hg)	120 (110–130)	120 (110–133)	120 (110–130)	120 (110–140)	0.06
NYHA class					
NYHA I/II	89%	82%	74%	77%	**<0.001**
NYHA III	8.7%	17%	24%	20%	**<0.001**
NYHA IV	2.0%	1.4%	2.2%	3.0%	0.39
Pharmacotherapy at hospital discharge					
Loop and/or thiazide diuretic	69%	78%	85%	76%	**<0.001**
Daily dose of loop diuretic (equivalent to furosemide dose)[c]	76 (±113) $n = 219$	62 (±88) $n = 560$	59 (±105) $n = 225$	54 (±53) $n = 234$	**0.02**
Aldosterone antagonist	35%	30%	47%	34%	**<0.001**
ACE-I or ARB	79%	72%	66%	72%	**0.001**
β-blocker	71%	70%	72%	67%	0.57
Calcium channel blocker	19%	27%	21%	23%	**0.005**

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
[a]P - for comparison between the four groups.
[b]In those who survived to hospital discharge.
[c]One milligram bumetanide = 20 mg torsemide = 40 mg furosemide.
Bolded font indicates p values of <0.5.

Table 4 Long-term outcomes of the four groups of patients with preserved ejection fraction

Variable	MIP restrictive/ pseudonormal	MIP other than restrictive/ pseudonormal	AF group	Grey area group	P^a
Lost to follow-up	2.2% 8/356	9.2% 73/797	7.1% 23/324	9.2% 34/371	**0.001**
All-cause death	19.5% 66/339	18.0% 126/699	22.3% 64/287	18.9% 61/322	0.49
Cardiovascular death	11.5% 39/339	8.6% 60/699	11.5% 33/287	10.9% 35/322	0.35
Non-cardiovascular death	2.4% 8/339	3.9% 27/699	5.6% 16/287	4.3% 14/322	0.22
Unknown cause of death	5.6% 19/339	5.6% 39/699	5.2% 15/287	3.7% 12/322	0.63
All-cause hospitalization	34.8% 118/339	40.1% 280/699	38.7% 111/287	38.8% 125/322	0.44
Cardiovascular (non-HF) hospitalization	9.1% 31/339	14.4% 101/699	15.7% 45/287	13.7% 44/322	**0.06**
Rehospitalization for HF	20.4% 69/339	16.3% 114/699	17.4% 50/287	15.8% 51/322	0.37
Non-cardiovascular hospitalization	7.7% 26/339	16.3% 114/699	11.1% 32/287	14.0% 45/322	**0.001**
All-cause death or rehospitalization for HF	32.4% 110/339	29.3% 205/699	36.2% 104/287	30.1% 97/322	0.18

AF, atrial fibrillation; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; MIP, mitral inflow pattern.
[a]P - for comparison between the four groups.
Bolded font indicates p values of <0.1.

pressure is to be expected on resting echocardiography, unless echocardiography is obtained after haemodynamics have improved with treatment. Lack of echocardiographic signs of elevated LA pressure should alert to other possible causes of acute dyspnoea. Echocardiographic estimation has proven a reliable tool to identify patients with elevated LA pressure, as verified by invasive measurements.[12–14] A full echocardiographic assessment of diastolic function and LV filling pressures involves a complex diagnostic algorithm with a central role of TDI-derived measurements (e', E/e') in recognizing

Figure 3 Long-term outcomes: event rates in the four groups of patients with preserved ejection fraction. For pairwise comparisons between groups, only *P* values of <0.1 are given (with *P* values of <0.05 marked in red). AF, atrial fibrillation; HF, heart failure; MIP, mitral inflow pattern.
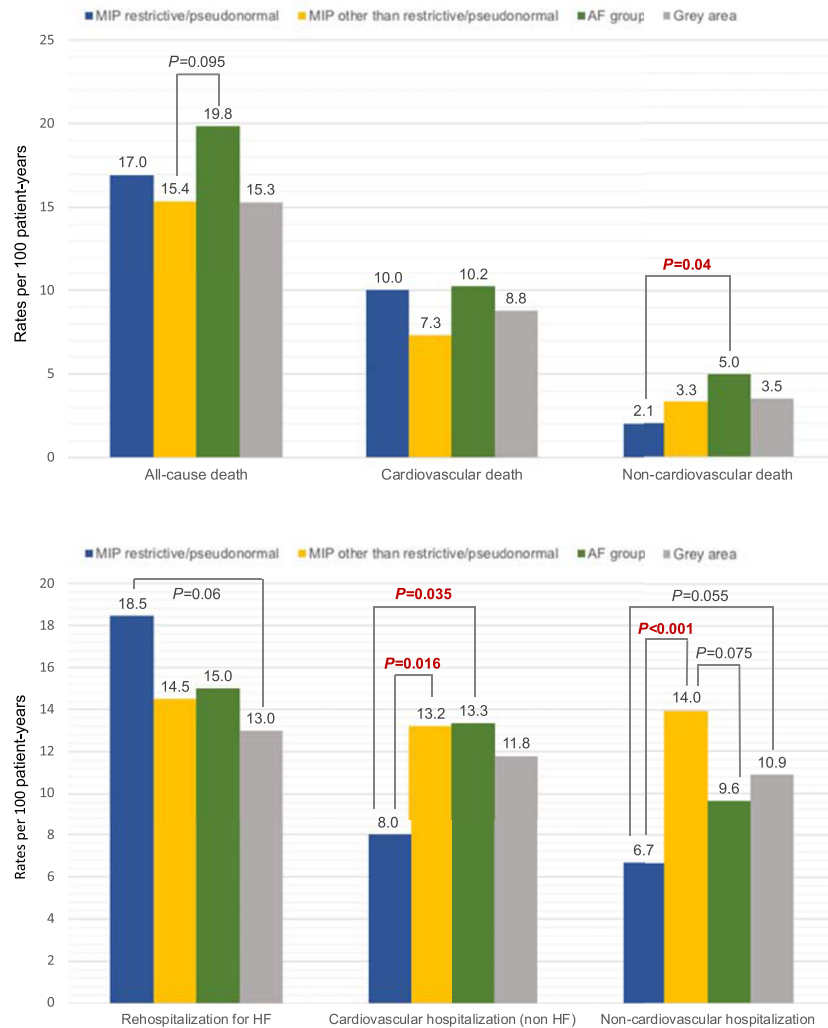

diastolic dysfunction; however, the final distinction between elevated and normal LA pressure and grading of diastolic dysfunction are largely based on MIP, with E/A ≥ 2 (consistent with 'restrictive' MIP) indicative of significantly increased LA pressure and grade III diastolic dysfunction, and E/A ≤ 0.8 indicative of normal LA pressure.[4] Patients with E/A ratio between 0.8 and 2 should be further assessed to discriminate between 'normal' and 'pseudonormal' (i.e. indicative of elevated LA pressure and grade II diastolic dysfunction) MIP. Although neither TDI-derived parameters nor TRV were gathered in the registry database, it is reasonable to assume that some investigators must have had access to those data allowing them to discriminate between patients with pseudonormal (classified as 'restrictive/pseudonormal' in the registry database) and normal (classified as 'other than restrictive/pseudonormal') MIP. Out of 1239 patients with MIP assessed, 1157 (93%) were allocated to the restrictive/pseudonormal or the 'other' MIP group by the investigators (possibly based also on echocardiographic parameters other than E/A ratio), and classification of MIP based merely on E/A ratio was performed only in the remaining 7%.

We included patients hospitalized for presumed acute HF, but MIP was restrictive/pseudonormal (indicative of elevated LA pressure) in only 29% of those with MIP assessed (19% of the whole HFpEF group) and other than restrictive/pseudonormal (indicative of normal LA pressure) in 64% of those with MIP assessed (43% of the whole group), suggesting that among the latter, acute HF presentation could potentially be attributable to reasons other than HF and that even if those patients indeed had chronic HFpEF, it may not have been the main reason for the present symptom exacerbation. However, contrary to our initial hypothesis, patients with MIP other than restrictive/pseudonormal (who potentially might have been misdiagnosed with HFpEF) were

Figure 4 Kaplan–Meier curves for patients with preserved, mid-range and reduced ejection fraction: (A) all-cause death, (B) all-cause death or rehospitalization for heart failure. HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; MIP, mitral inflow pattern; r/p, restrictive/pseudonormal.
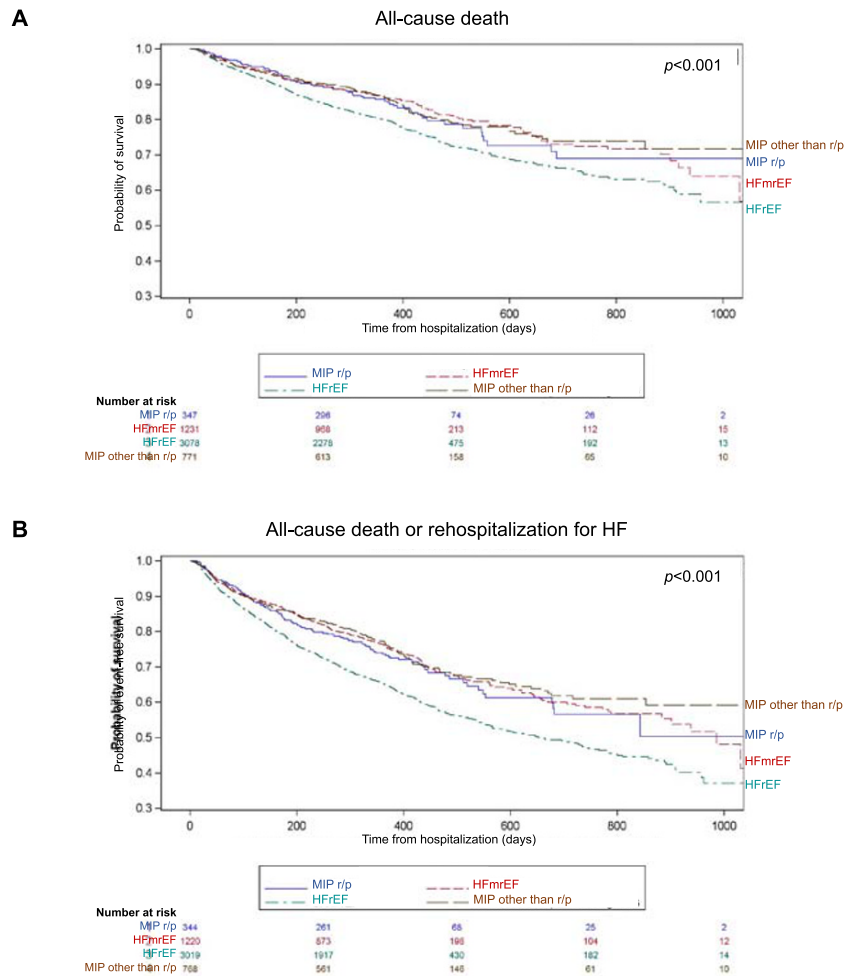
characterized by fewer concomitant cardiac and non-cardiac comorbidities than patients with restrictive/pseudonormal MIP. A high prevalence of comorbidities is expected in HFpEF,[1,8,24,25] but we expected it to be even higher in patients potentially misdiagnosed with HFpEF. Nevertheless, in long-term follow-up, despite fewer non-cardiac comorbidities reported at baseline, patients with MIP other than restrictive/pseudonormal (i.e. potentially misdiagnosed with HFpEF) had twice as many non-cardiovascular hospitalizations as patients with restrictive/pseudonormal MIP, which is more consistent with non-HF causes of frailty and symptoms mistaken for HF and a pattern previously described,[26] and might indicate that at least some of those patients did have some relevant comorbidities that had not yet been recognized at the time of the index hospitalization. This underlines the need for careful assessment of elderly patients presenting with dyspnoea, impaired exercise tolerance, or oedema, for

hitherto unknown comorbidities that could either imitate or exacerbate HF symptoms.

Conversely, in long-term follow-up, patients with restrictive/pseudonormal MIP tended to experience the composite endpoint of death or HF rehospitalization more often, although the difference did not reach statistical significance. Moreover, patients with EF $\geq$ 50% and restrictive/pseudonormal MIP had a significantly higher risk for all-cause death or HF rehospitalization than HFmrEF patients, which might be regarded as a 'post-factum' validation of their initial HF diagnosis. Compared with patients with MIP suggestive of normal LA pressure, patients with restrictive/pseudonormal MIP had more severe HF symptoms at hospital admission (with higher heart rate, higher New York Heart Association class and more pulmonary congestion), and on echocardiography—larger LAVI and higher prevalence of moderate-to-severe mitral and

tricuspid regurgitation. Despite the same frequency of diuretic therapy during hospitalization, patients with restrictive/pseudonormal MIP experienced more significant improvement in HF symptoms than patients with other MIP —possibly because they were correctly diagnosed and adequately treated. Indeed, the sole 2016 ESC recommendation on HFpEF treatment concerns diuretic therapy to alleviate symptoms.[1] Taken together, these findings suggest that echocardiographically assessed elevation of resting LA pressure may not suffice to diagnose HFpEF but can identify patients with more severe HF and with greater risk of HF events.

Elevated LA pressure, estimated echocardiographically, has been previously linked to unfavourable outcomes in HF.[27–31] However, echocardiographic indices of diastolic dysfunction and elevated LA pressure might not directly translate into reduced survival in HFpEF, partly because of their poor correlation with factual LV filling pressures, but also because HFpEF pathophysiology seems to be related not only to diastolic but also preclinical systolic dysfunction.[32–35]

In our study, we analysed patients with AF during echocardiography as a separate group. Importantly, approximately one third of patients in both restrictive/pseudonormal MIP and other MIP group had AF at hospital admission but converted to sinus rhythm by the time of echocardiographic evaluation (which enabled assessment of MIP). Atrial fibrillation may be regarded as a confounder in HFpEF, first, because it can lead to HF symptoms and elevation in natriuretic peptides even in patients without HF, and second, because it hinders echocardiographic assessment of diastolic function. On the other hand, AF has the same risk factors as HFpEF and is highly prevalent in HFpEF; in the ESC-HF LT Registry, AF was present in 39% of HFpEF patients, and in 27% of HFrEF patients,[17] and in the less selective Swedish Heart Failure Registry, AF was present in 65% in HFpEF, 60% in HFmrEF, and 53% in HFrEF.[36] Furthermore, AF may be an important exacerbating factor in chronic HF, as well as a cause of tachycardia-induced cardiomyopathy. In HFpEF, AF was related to worse cardiovascular and all-cause outcomes.[17,36] In our study, crude rates of all-cause and cardiovascular mortality, as well as all-cause hospitalizations were similar for all four analysed groups.

Interestingly, 73% of patients with preserved EF and acute symptoms requiring hospitalization did not have their HF diagnosis verified during the index hospitalization, with a vast majority lacking even a simple measurement of natriuretic peptides. Naturally, this might result from the fact that approximately 30% were diagnosed with HFpEF previously. Many of those patients might indeed have chronic HFpEF; however, this does not necessarily mean that HF was responsible for their current decompensation. In fact, once 'labelled' with an HF diagnosis, those patients were potentially more likely to have their subsequent symptoms automatically attributed to HF. Furthermore, some previous data suggest that in everyday clinical practice, HF may be overdiagnosed in 16–

46% of patients.[11,26,37,38] In our study, half of patients in whom the 2016 ESC definition was assessed did not meet those relatively 'mild' diagnostic criteria for HFpEF (elevated natriuretic peptides, and at least one of the three: presence of LV hypertrophy, enlarged LA, or diastolic dysfunction). Almost half of the 92% of patients in whom LV hypertrophy was assessed had normal LV wall thickness, which is striking, given that hypertensive LV hypertrophy in the elderly is the most common cause of diastolic dysfunction and HFpEF. Finally, 43% of the whole group had MIP other than restrictive/pseudonormal, suggesting normal LA pressure, despite acute symptom exacerbation.

The lack of a single, universal HFpEF definition, as well as the fact that no treatment has yet been shown to improve survival in HFpEF, implies that we still fail to properly define and diagnose HFpEF. The results of our study, on one hand, show that securing acute HFpEF diagnosis with objective evidence from biomarker measurements and echocardiography may often be neglected in clinical practice but, on the other hand, might reflect limitations of the tested definition itself. A good HFpEF definition should facilitate estimation of risk of future HF events and might originate from on-going or forthcoming clinical trials, especially if they yield positive results in terms of HFpEF therapy. For now, the HFA-PEFF stepwise approach, integrating functional, morphological, and biomarker assessment, with evaluation both at rest and, in cases of uncertainty, during exercise, might prove the most reliable of different HFpEF diagnostic criteria.[3]

Limitations of the study

The limitations of our study arise mainly from the type of data (i.e. registry-based). We had access only to MIP for LA pressure estimation (and, consequently, for assessment of LV diastolic dysfunction), as neither TDI-derived parameters (e', E/e') nor TRV were collected in the registry. Applying MIP as a sole indicator of LA pressure does not well distinguish between patients with elevated and normal LA pressure. However, no single echocardiographic parameter is fully accurate in LA pressure estimation, and even E/e' ratio shows relatively poor correlation with pressures measured in invasive hemodynamic studies.[33,39,40] Thus, according to both the ASE/EACVI guidelines[4] and the HFA-PEFF algorithm,[3] the diagnosis of diastolic dysfunction does not rely on a single echocardiographic parameter but involves a complex algorithm. According to the ASE/EACVI guidelines, while E/e' ratio (together with e', LAVI and TRV) is used for the diagnosis of diastolic dysfunction in patients with normal EF, MIP (E/A) is the major parameter used for its grading and LA pressure estimation.[4] A number of factors may influence MIP, including severe valvular disease (especially severe mitral regurgitation), right ventricular dysfunction, pericardial diseases, arrhythmias, and conductance disturbances. We have not

excluded such patients from our study (partly because it was impossible to identify all of the potential confounders, for example, no data on right ventricular function, pericardial diseases, or atrioventricular block were gathered in the Registry; based on data collected in the Registry, it was impossible to discriminate between severe and moderate valvular disease). Instead, we have distinguished the AF group and the grey area group, which included patients in whom MIP was either not assessed or could not have been assessed due to potential confounders. Despite its limitations, MIP has proven useful in clinical practice, for example, for differential diagnosis of acute dyspnoea, as well as for guiding diuretic therapy or optimizing LV assist devices settings in HF patients.[12,14,41] Pseudonormal or restrictive MIP has also been shown to predict poor prognosis in HF patients.[29–31] Although data from right heart catheterization were gathered in the registry, the study was performed only in 1.6% patients and thus could not be used for LA pressure classification in our analysis. Information on LV hypertrophy was reported at the discretion of investigators as either 'yes' or 'no', with no data on LV mass index gathered in the survey. Furthermore, a large portion of data on LAVI and natriuretic peptides was missing. Thus, the actual number of patients fulfilling the 2016 ESC HFpEF criteria[1] or the 2016 echocardiographic definition of diastolic dysfunction[4] was impossible to determine. Furthermore, the 2016 ESC HFpEF definition applied in this analysis may be considered a combination of acute (natriuretic peptides) and chronic HF criteria (e.g. a cut-off for LAVI in acute HFpEF might be higher due to hypervolemia). Next, no information on the exact time point of echocardiographic evaluation was given in the registry, and it is possible that in a substantial portion of patients with LA pressure elevated on hospital admission, it normalized with diuretic treatment by the time of echocardiographic examination and MIP assessment. Still, restrictive/pseudonormal MIP at the time of echocardiographic evaluation indicative of elevated LA pressure persisting after several days of treatment might reflect a more advanced disease. In a study by Okura et al., in patients with congestive HFpEF and LA pressure estimated on echocardiography, LA pressure elevated after medical therapy independently predicted death or unplanned HF hospitalization, while initially elevated LA pressure did not.[32] Furthermore, in patients with no orthopnoea/resting dyspnoea, echocardiography at rest may show normal LA pressure even in the presence of HFpEF; thus, some patients with MIP other than restrictive/pseudonormal might, in fact, have had HFpEF. In some patients, the diagnosis of HFpEF might have been made before the index hospitalization. Also, there was no information on the actual heart rhythm during the echocardiographic study, and allocation to the AF group was based on the presence of AF on the available electrocardiograms and a lack of MIP assessment on echocardiography. However, we created the AF group primarily to assess the proportion of patients in whom lack of data on MIP might have been 'justified'.

Causes of subsequent re-hospitalizations were allocated by investigators based on their clinical judgement, and thus, HF rehospitalizations might have potentially been misclassified. Finally, a small proportion of patients (7.5%) were lost to follow-up: significantly fewer patients were lost to follow-up in the restrictive/pseudonormal MIP group (2.2%, $P < 0.001$) compared with the remaining three groups (9.2%, 7.1% and 9.2% in the other MIP, 'AF' and grey area group, respectively).

Conclusions

In clinical practice, a diagnosis of acute HFpEF appears to be made clinically rather than by natriuretic peptides and echocardiography. Assessment of the 2016 ESC HFpEF criteria was possible only in a quarter of hospitalized patients with preserved EF, and in this quarter, only half met the 2016 ESC criteria for HFpEF. In patients hospitalized for presumed acute HFpEF in whom MIP was assessed, less than one third had echocardiographic signs of elevation of estimated LA pressure (restrictive/pseudonormal MIP), and two thirds had presumably normal LA pressure (MIP other than restrictive/pseudonormal). This might be explained by acute HFpEF misdiagnosis, but also by echocardiography having been performed after clinical stabilization and normalization of filling pressures, or by AF that subsequently converted to sinus rhythm. Despite fewer non-cardiac comorbidities reported at baseline, patients with presumably normal LA pressure (MIP other than restrictive/pseudonormal) had higher risk for subsequent non-cardiovascular and cardiovascular non-HF hospitalizations, while those with restrictive/pseudonormal MIP (suggestive of elevated LA pressure) had a trend towards higher risk of death or HF rehospitalization in long-term follow-up. This underscores the need for accurate and objective verification of clinical HF diagnosis and careful screening for comorbidities in patients with preserved EF presenting with symptoms suggestive of HF.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. EORP Oversight Committee, Steering Committee and Investigators of the Registry

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis

and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: 1810–1852.

3. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**: 3297–3317.

4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1321–1360.

5. Liu M, Fang F, Yu CM. Noncardiac comorbidities in heart failure with preserved ejection fraction—commonly ignored fact. *Circ J* 2015; **79**: 954–959.

6. Streng KW, Nauta JF, Hillege HL, Anker SD, Cleland JG, Dickstein K, Filippatos G, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, van der Meer P, Voors AA. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. *Int J Cardiol* 2018; **271**: 132–139.

7. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. *Circ Heart Fail* 2011; **4**: 538–540.

8. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? *J Am Coll Cardiol* 2012; **60**: 2349–2356.

9. Oikonomou E, Chrysohoou C, Tousoulis D. Heart failure a cluster of comorbidities or a unique entity? *Int J Cardiol* 2019; **277**: 196–197.

10. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013; **15**: 1173–1184.

11. Kapłon-Cieślicka A, Tymińska A, Peller M, Balsam P, Ozierański K, Galas M, Marchel M, Crespo-Leiro MG, Maggioni AP, Drożdż J, Filipiak KJ, Opolski G. Diagnosis, clinical course and one-year outcome in patients hospitalized for heart failure with preserved ejection fraction (from the Polish Cohort of the ESC-HF Long-Term Registry). *Am J Cardiol* 2016; **118**: 535–542.

12. Mitter SS, Shah SJ, Thomas JD. A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. *J Am Coll Cardiol* 2017; **69**: 1451–1464.

13. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017; **69**: 1937–1948.

14. Frea S, Centofanti P, Pidello S, Giordana F, Bovolo V, Baronetto A, Franco B, Cingolani MM, Attisani M, Morello M, Bergerone S, Rinaldi M, Gaita F. Noninvasive assessment of hemodynamic status in HeartWare left ventricular assist device patients: validation of an echocardiographic approach. *JACC Cardiovasc Imaging* 2019; **12**: 1121–1131.

15. Jondeau G, Detaint D, Arnoult F, Phan G, Morgan C, Mercadier JJ, Aumont MC. Acute heart failure: how to evaluate left ventricular filling pressure in practice? *Arch Cardiovasc Dis* 2009; **102**: 319–326.

16. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.

17. Zafir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, De Mora Martin M, Polonski L, Silva-Cardoso J, Amir O, ESC-HFA HF Long-Term Registry Investigators. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018; **39**: 4277–4284.

18. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJV. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. *JACC Heart Fail* 2017; **5**: 471–482.

19. National Institutes of Health. EMPagliflozin outcomE tRial in Patients WithchrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). ClinicalTrials.gov Identifier: NCT03057951.

20. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392.

21. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.

22. Carson PE, Anand IS, Win S, Rector T, Haass M, Lopez-Sendon J, Miller A, Teerlink JR, White M, McKelvie RS, Komajda M, Zile MR, McMurray JJ, Massie B. The hospitalization burden and post-hospitalization mortality risk in heart failure with preserved ejection fraction: results from the I-PRESERVE trial (Irbesartan in heart failure and preserved ejection fraction). *JACC Heart Fail* 2015; **3**: 429–441.

23. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; **138**: 861–870.

24. Tang L, Wu YY, Lip GY, Yin P, Hu Y. Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol* 2016; **3**: e30–e44.

25. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006; **48**: 1527–1537.

26. Carey SA, Bass K, Saracino G, East CA, Felius J, Grayburn PA, Vallabhan RC, Hall SA. Probability of accurate heart failure diagnosis and the implications for hospital readmissions. *Am J Cardiol* 2017; **119**: 1041–1046.

27. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, Desai AS, Heitner JF, Li G, Fang J, Rouleau J, Zile MR, Markov V, Ryabov V, Reis G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail* 2014; **7**: 740–751.

28. Donal E, Lund LH, Oger E, Hage C, Persson H, Reynaud A, Ennezat PV, Bauer F, Drouet E, Linde C, Daubert C, KaRen investigators. New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) Study. *Eur J Heart Fail* 2015; **17**: 680–688.

29. Lee JG, Beom JW, Choi JH, Kim SY, Kim KS, Joo SJ. Pseudonormal or restrictive filling pattern of left ventricle predicts poor prognosis in patients with ischemic heart disease presenting as acute heart failure. *J Cardiovasc Imaging* 2018; **26**: 217–225.

30. Rigolli M, Rossi A, Quintana M, Klein AL, Yu CM, Ghio S, Dini FL, Prior D, Troughton RW, Temporelli PL, Poppe KK, Doughty RN, Whalley GA, MeRGE Collaborators. The prognostic impact of diastolic dysfunction in patients with chronic heart failure and post-acute myocardial infarction: can age-stratified E/A ratio alone predict survival? *Int J Cardiol* 2015; **181**: 362–368.

31. Somaratne JB, Whalley GA, Poppe KK, Gamble GD, Doughty RN. Pseudonormal mitral filling is associated with similarly poor prognosis as restrictive filling in patients with heart failure and coronary heart disease: a systematic review and meta-analysis of prospective studies. *J Am Soc Echocardiogr* 2009; **22**: 494–498.

32. Okura H, Kubo T, Asawa K, Toda I, Yoshiyama M, Yoshikawa J, Yoshida K. Elevated E/E' predicts prognosis in congestive heart failure patients with preserved systolic function. *Circ J* 2009; **73**: 86–91.

33. Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H. Diagnostic accuracy of tissue doppler index E/e' for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: a systematic review and meta-analysis. *J Am Heart Assoc* 2016; **5** pii: e002530.

34. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD, PARAMOUNT Investigators. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014; **63**: 447–456.

35. Morris DA, Ma XX, Belyavskiy E, Aravind Kumar R, Kropf M, Kraft R, Frydas A, Osmanoglou E, Marquez E, Donal E, Edelmann F, Tschöpe C, Pieske B, Pieske-Kraigher E. Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. *Open Heart* 2017; **4**: e000630.

36. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2017; **5**: 565–574.

37. Verdú-Rotellar JM, Frigola-Capell E, Alvarez-Pérez R, da Silva D, Enjuanes C, Domingo M, Mena A, Muñoz MA. Validation of heart failure diagnosis registered in primary care records in two primary care centres in Barcelona (Spain) and factors related. A cross-sectional study. *Eur J Gen Pract* 2017; **23**: 107–113.

38. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. *Clin Epidemiol* 2010; **2**: 235–239.

39. Santos M, Rivero J, McCullough SD, West E, Opotowsky AR, Waxman AB, Systrom DM, Shah AM. E/e' ratio in patients with unexplained dyspnea: lack of accuracy in estimating left ventricular filling pressure. *Circ Heart Fail* 2015; **8**: 749–756.

40. Broch K, Al-Ani A, Gude E, Gullestad L, Aakhus S. Echocardiographic evaluation of left ventricular filling pressure in heart transplant recipients. *Scand Cardiovasc J* 2014; **48**: 349–356.

41. Logeart D, Saudubray C, Beyne P, Thabut G, Ennezat PV, Chavelas C, Zanker C, Bouvier E, Solal AC. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. *J Am Coll Cardiol* 2002; **40**: 1794–1800.