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ORIGINAL RESEARCH ARTICLE

Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: a systematic review and meta-analysis

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Abstract

Aims This study aimed to assess by a meta-analysis the clinical characteristics, all-cause and cardiovascular mortality, and hospitalization of patients with heart failure (HF) with mid-range ejection fraction (HFmrEF) compared with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Methods and results Data from 12 eligible observational studies including 109 257 patients were pooled. HFmrEF patients were significantly different and occupied a mid-position between HFrEF and HFpEF: mean age 73.6 ± 9.8 vs. 72.6 ± 9.8 and 77.6 ± 7.2 years, male gender 59% vs. 68.5% and 40%, ischaemic heart disease 49% vs. 52.6% and 39.4%, hypertension 67.3% vs. 61.5% and 76.5%, atrial fibrillation 45.2% vs. 39.6% and 46%, chronic obstructive pulmonary disease 26.4% vs. 24.9% and 30.5%, estimated glomerular filtration rate 62 ± 30 vs. 63.3 ± 23 and 59 ± 22.5, use of renin–angiotensin system inhibitors 79.6% vs. 90.1% and 68.7%, beta-blockers 82% vs. 89% and 73.5%, and aldosterone antagonists 20.3 vs. 31.5% and 26%, *P*-values < 0.05. After a mean follow-up of 31 ± 5 months, all-cause mortality was significantly lower in HFmrEF than in HFrEF and HFpEF (26.8% vs. 29.5% and 31%): risk ratio (RR) 0.95 [0.93–0.98; 95% confidence interval (CI)], $P < 0.001$, and 0.97 (0.94–0.99; 95% CI), $P = 0.014$, respectively. Cardiovascular mortality was lowest in HFmrEF (9.7% vs. 13% and 12.8%): RR = 0.81 (0.73–0.91), $P < 0.001$, and 1.10 (0.97–1.24; 95% CI), $P = 0.13$, respectively. HF hospitalization in HFmrEF compared to that in HFrEF and HFpEF was 23.9% vs. 27.6% and 23.3% with RR = 0.89 (0.85–0.93), $P < 0.001$, and RR = 1.12 (1.07–1.17), $P < 0.001$, respectively.

Conclusions The results of this study support that HFmrEF is a distinct category characterized by a mid-position between HFrEF and HFpEF and with the lowest all-cause and cardiovascular mortality.

Keywords Heart failure; Ejection fraction; Mid-range; Borderline

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Introduction

During the last three decades, left ventricular systolic ejection fraction (LVEF) has been used as the main diagnostic and prognostic parameters in management of patients with chronic heart failure (CHF). Reduced LVEF is generally associated with increased risk of overt heart failure (HF) and worse prognosis, but the majority of randomized controlled trials using therapeutic or mechanical interventions has been restricted to CHF patients with LVEF <35%. Nonetheless, observational studies on patients with mildly reduced LVEF have shown poorer prognosis compared with those with HF and normal LVEF.[1,2]

Until recently, CHF patients have been classified into two categories: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) based on LVEF estimation with cut-off limits of ≤40% and ≥50%, respectively. However, grey-area patients with moderately impaired LVEF

have not been comprised in these traditional categories and have been poorly characterized. Recently, more attention has been given to patients with borderline low systolic LVEF, whereas both the European Society of Cardiology and American Society of Cardiology have introduced a new category of CHF with borderline reduced LVEF of 40–49%, called HF with mid-range ejection fraction (HFmrEF).[3,4]

Despite publication of a considerable number of epidemiological studies and reviews on patients with HFmrEF compared with HFrEF and HFpEF, the clinical characteristics and prognosis of this newly suggested entity are still inadequately addressed and the results concerning mortality and hospitalization have varied considerably across the published studies.[5–7] By means of a systematic review and meta-analysis of the current literature, we collected and pooled all available published data in order to shed more light on patient characteristics, mortality, and hospitalization of HFmrEF patients compared with the established categories HFrEF and HFpEF.

Methods

Study design

This is a systematic literature review and meta-analysis, which was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis.[8]

Search strategy

The search was conducted in the electronic databases PubMed and Web of Science for all published clinical studies that examined baseline characteristics and mortality in patients with HFmrEF compared with HFrEF and HFpEF. The following keywords in different combinations were used: heart failure, left ventricle, ejection fraction combined with the terms mid-range and borderline. All electronically published papers were screened by titles and abstracts and by reviewing the full paper if deemed relevant. The literature search was restricted to papers published until 30 September 2017. The systematic search was supplemented by reviewing all references in retrieved eligible studies, as well as key review papers.

Study eligibility

Observational studies and randomized controlled trials were considered for inclusion if they reported key baseline characteristics and all-cause mortality in patients with HFmrEF (defined as LVEF of 40–49%) compared with HFrEF (defined as LVEF $<$40%) and HFpEF (defined as LVEF $\geq$50%). The diagnosis of HF categories should rely on the recent transthoracic echocardiographic findings and clinical judgement according to the guidelines. Eligible studies were also required to provide numbers of events for all-cause and cardiovascular mortality, and preferably HF-specific hospitalization with a follow-up period of at least 1 year. We excluded all studies with a follow-up period shorter than 1 year, small-sized studies including $<$100 participants, and studies with insufficiently reported data.

Data extraction

We extracted data on the demographic features and key baseline clinical variables reported as means or medians with standard deviations (SD) or ranges from each study. We extracted absolute numbers for all-cause and cardiovascular mortality and HF hospitalization. Values reported as medians with ranges were re-estimated to their corresponding means with SDs. Values presented as percentages were recalculated to absolute numbers. In one study, [7] the death and hospitalization numbers were approximated from the Kaplan–Meier curve. In case of studies lacking key data in published reports, we contacted the corresponding authors to request the missing information. Two authors (J. A. and J. L.) conducted the search and data extraction independently. Any disagreement was resolved by consensus.

Statistical methods

Baseline characteristics were pooled and analysed as either weighted means or numbers. The weighted mean difference method was used for pooling of means and their SDs. The reported numbers of all-cause and cardiovascular mortality and HF hospitalization in eligible studies were pooled for the HFmrEF vs. HFrEF and HFpEF groups, followed by an estimation of a risk ratio (RR) with 95% confidence interval (CI). Despite the significant heterogeneity between studies, we used a fixed-effects model in order to maintain the real sizes of the larger studies but beside that presented the results of random-effects methods wherever reasonable. For the overall estimated RR, a P-value $<$0.05 was considered statistically significant. Heterogeneity among studies was tested using the χ^2 method (P-values $<$0.05 were considered statistically significant) and the I^2 statistic. The I^2 ranging between 0% and 100% indicated the percentage of variation in the study results attributable to between-study heterogeneity rather than due to sampling error, and an I^2 value $>$20% was considered statistically significant. All analyses were performed using the meta-analysis package of the statistic software program STATA Version 13 (STATA Corporation, Lakeway Drive, College Station, TX).

Results

Twelve eligible observational studies were included in this meta-analysis. The search process and outputs are shown in *Figure 1*.

Study and patient characteristics

Study characteristics are shown in *Table 1*. The included studies were either registry or retrospective data analyses of previously conducted prospective trials. Of a total population of 109 257 patients, 51 496 (47.1%) had HFrEF, 20 114 (18.4%) had HFmrEF, and 37 647 (34.4%) had HFpEF. Patients were followed up for at least 12 months with a mean period of 31 ± 5 months.

Baseline characteristics of the three HF categories are reported in *Table 2*. There were statistically significant differences between HFmrEF and HFrEF and between HFmrEF and HFpEF. Patients with HFmrEF were older than those with HFrEF but younger than those with HFpEF. The proportion of males and prevalence of ischaemic heart disease (IHD) among HFmrEF were lower than those among HFrEF, but higher than those among HFpEF. Hypertension was more frequent in patients with HFmrEF than in those with HFrEF, but less frequent than in those with HFpEF. Diabetes was significantly less frequent in both HFmrEF and HFrEF than in HFpEF. Atrial fibrillation was more frequently present among HFmrEF than among HFrEF but less frequent than among HFpEF. The prevalence of chronic obstructive pulmonary disease (COPD) was highest in HFpEF relative to both HFrEF and HFmrEF. HFpEF patients had also significantly worse renal function than patients with HFrEF and HFmrEF. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers were more frequently used in HFrEF than in both HFmrEF and HFpEF. Aldosterone antagonists were used more frequently in patients with HFpEF than in both those with HFrEF and HFmrEF.

Meta-analysis of risk of all-cause mortality

At the end of follow-up, patients with HFmrEF had lower all-cause mortality 5402/20 114 (26.8%) than those with HFrEF 15 222/51 496 (29.5%) and those with HFpEF 11 681/37 647 (31.0%). Pooled data of the 12 studies using the fixed-effects model showed that the risk of all-cause death was significantly lower in patients with HFmrEF than in those with HFrEF with RR = 0.95 (0.93–0.98; 95%CI), $P < 0.001$, and HFpEF with RR = 0.97 (0.94–0.99; 95%CI), $P = 0.020$ (*Figure 2*. There was significant heterogeneity between the included studies, $P < 0.001$ and $I^2 > 20\%$. Running the analysis using the

Figure 1 Flow chart of search process and results.

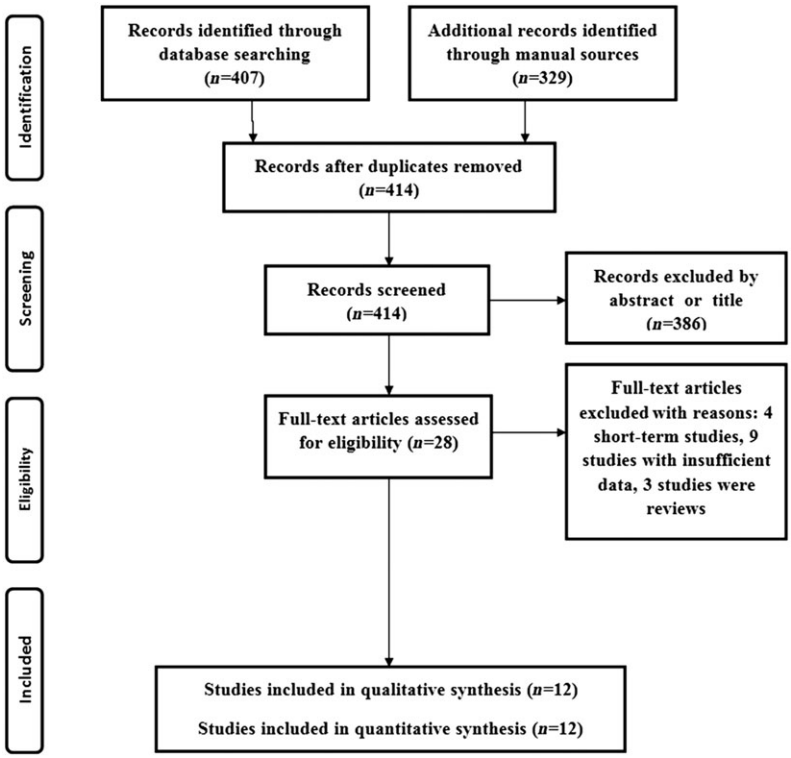


Table 1 Characteristics of the included studies

Author and publication year	Study type	Number of patients				Mean follow-up (months ± SD)
		All	HFrEF	HFmrEF	HFpEF	
Cheng *et al.*,[5] 2014	Hospital registry data retrospective analysis	40.239	15.716	5.626	18.897	12 ± NA
Junior *et al.*,[22] 2016	Patients referred for exercise testing; retrospective analysis	774	620	107	47	52 ± 9.5
Delepaul *et al.*,[26] 2017	HF unit care registry; retrospective analysis	482	258	115	109	32 ± 14.5
Gomez-Otero *et al.*,[11] 2017	Prospective registry data	1.420	583	227	610	12 ± NA
Chioncel *et al.*,[6] 2017	Prospective registry data	9.134	5.460	2.212	1.462	12 ± NA
Rickenbacher *et al.*,[15] 2017	Prospective randomized trial; retrospective analysis	622	402	108	112	27 ± 8
Pascual-Figal *et al.*,[14] 2017	Prospective cohorts of ambulatory patients	3.446	2.351	460	635	41.5 ± 3.5
Koh *et al.*,[18] 2017	Swedish National Registry; retrospective analysis	42.061	23.402	9.019	9.640	36 ± 12
Coles *et al.*,[10] 2017	Hospitals registry; retrospective analysis	4.025	1414	521	2090	12 ± NA
Bonsu *et al.*,[13] 2017	Hospitals registry; retrospective analysis	1.488	345	265	878	60 ± NA
Margolis *et al.*,[12] 2017	Patients admitted with STEMI and underwent PCI	2.086	215	858	1013	42 ± 30
Tsuji *et al.*,[7] 2017	Multicentre prospective observational study	3480	730	596	2154	36 ± NA

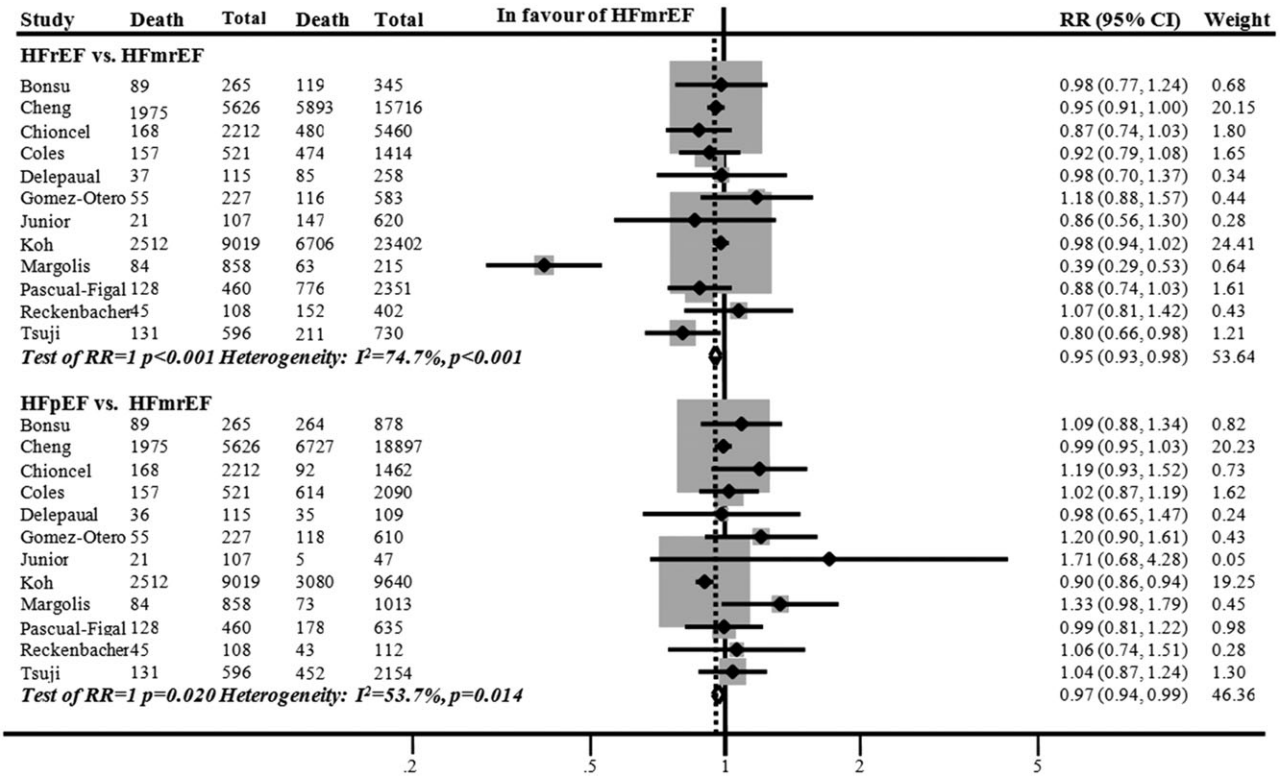
HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction.

Table 2 Comparison of baseline characterizes of heart failure with mid-range left ventricular ejection fraction with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

Characteristics	Number of studies providing data	Values shown as weighted means ± SD or numbers (%)			*P*-values	
		HFrEF	HFmrEF	HFpEF	HFmrEF vs. HFrEF	HFmrEF vs. HFpEF
Demographic and clinical characteristics						
Age (years)	12	72.3 ± 9.3	73.6 ± 9.8	77.6 ± 7.2	<0.001	<0.001
Male gender	12	35 259/51 496 (68.5%)	11 950/20 114 (59%)	15 211/37 647 (40%)	<0.001	<0.001
Ischaemic heart disease	12	27 091/51 496 (52.6%)	9918/20 114 (49%)	14 842/37 647 (39.4%)	0.034	<0.001
History of hypertension	12	31 691/51 496 (61.5%)	13 536/20 114 (67.3%)	28 824/37 647 (76.5%)	<0.001	<0.001
History of diabetes	12	16 139/51 496 (31.3%)	6079/20 114 (30.2%)	12 545/37 647 (33.3%)	0.17	0.021
History of atrial fibrillation	11	20 317/51 281 (39.6%)	8709/19 256 (45.2%)	16 857/36 634 (46%)	<0.001	<0.001
Chronic obstructive pulmonary disease	9	12 006/48 200 24.9%	4810/18 200 26.4%	10 322/33 845 30.5%	0.001	<0.001
Estimated glomerular filtration rate	6	63.3 ± 23	62.0 ± 30.0	59.0 ± 22.5	0.001	<0.001
Mean baseline LVEF	8	26.3 ± 4.2	43.1 ± 2.7	59.8 ± 3.6	<0.001	<0.001
Medications used						
ACEI/ARB	10	41 329/45 821 (90.1%)	13 575/17 044 (79.6%)	24 175/35 172 (68.7%)	<0.001	<0.001
Beta-blockers	10	40 429/45 821 (89%)	13 917/17 044 (82%)	25 711/35 172 (73.5%)	<0.001	<0.001
Aldosterone antagonists	10	14 419/45 821 31.5%	3475/17 044 20.3%	10 357/34 407 26.0%	<0.001	<0.001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; SD, standard deviation.

Figure 2 Meta-analysis of all-cause mortality comparing heart failure (HF) with mid-range ejection fraction (HFmrEF) with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFPEF). CI, confidence interval; RR, risk ratio.



random-effects model showed that the risk of all-cause death was still significantly lower in patients with HFmrEF than in those with HFrEF with RR = 0.90 (0.83–0.98; 95% CI), $P = 0.010$, but not significant when compared with those with HFpEF with RR = 1.01 (0.96–1.10; 95%CI), $P = 0.59$.

Data from five large size studies[5,6,9–11] including 94 981 patients were also pooled to estimate 1 year all-cause mortality. There were 14 078/46 126 (30.5%) deaths in HFrEF, 4876/16 936 (28.8%) in HFmrEF, and 10 740/31 919 (33.6%) in HFpEF. Using the fixed-effects model, the risk of all-cause mortality in the first year of follow-up was RR = 0.96 (0.94–0.99; 95% CI), $P = 0.013$, and RR = 0.94 (0.91–0.97; 95%CI), $P < 0.001$, comparing HFmrEF with HFrEF and HFpEF, respectively.

A sensitivity analysis was performed by excluding the relatively small study by Margolis *et al*.[12] due its larger effect in order to exclude the small-study effect. The results were unchanged when comparing HFmrEF with HFrEF and HFpEF.

Meta-analysis of risk of cardiovascular death

Five studies provided data for cardiovascular death.[6,7,11,13,14] There were 1229/9469 (13%) deaths among HFrEF patients, 365/3760 (9.7%) among HFmrEF patients, and 735/5739 (12.8%) among HFpEF patients. Meta-analysis using the fixed-effects model showed a significant lower risk of death in patients with HFmrEF than in those with HFrEF, RR = 0.81 (0.73–0.91; 95% CI), but no significant difference when compared with HFpEF, RR = 1.10 (0.97–1.24; 95% CI) (*Figure 3*). The results were unchanged using the random-effects model.

Meta-analysis of risk of heart failure hospitalizations

Five studies provided data for HF hospitalization.[5–7,11,15] There were 6319/22 891 (27.6%) hospitalizations among HFrEF patients, 2094/8769 (23.9%) among HFmrEF patients, and 5445/2323 (23.3%) among HFpEF patients. When data are pooled using the fixed-effects model, the risk of hospitalization was significantly lower in HFmrEF than in HFrEF but higher in HFpEF, RR = 0.89 (0.85–0.93; 95% CI), $P < 0.001$, and 1.12 (1.07–1.17; 95% CI), $P < 0.001$, respectively (*Figure 4*). It was not relevant to repeat the analysis using the random-effects model due to the large study effect.

All findings of the baseline characteristics, all-cause and cardiovascular mortality, and hospitalization are summarized in *Figures 5* and *6*.

Figure 3 Meta-analysis of cardiovascular death comparing heart failure (HF) with mid-range ejection fraction (HFmrEF) with HF with reduced ejection fraction (HFrEF) and HF preserved ejection fraction (HFPEF). CI, confidence interval; RR, risk ratio.

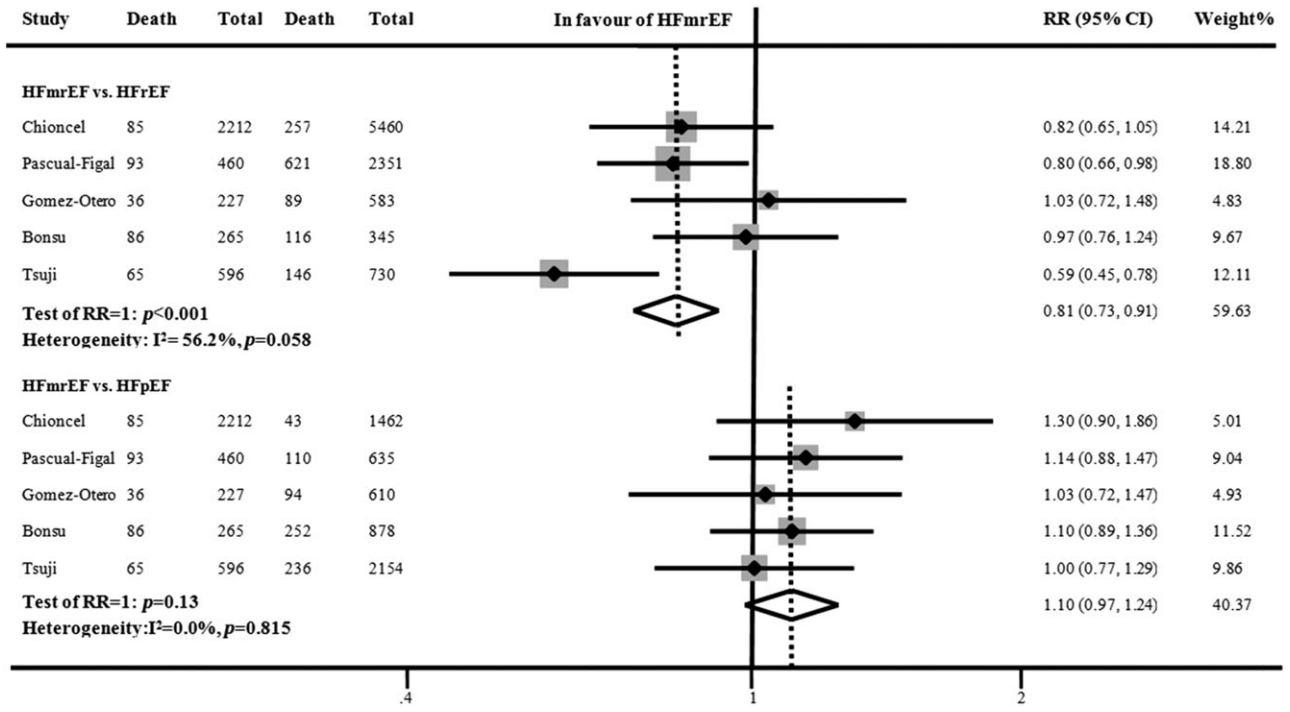


Figure 4 Meta-analysis of heart failure (HF) hospitalization comparing heart failure with mid-range ejection fraction (HFmrEF) with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFPEF). CI, confidence interval; RR, risk ratio.

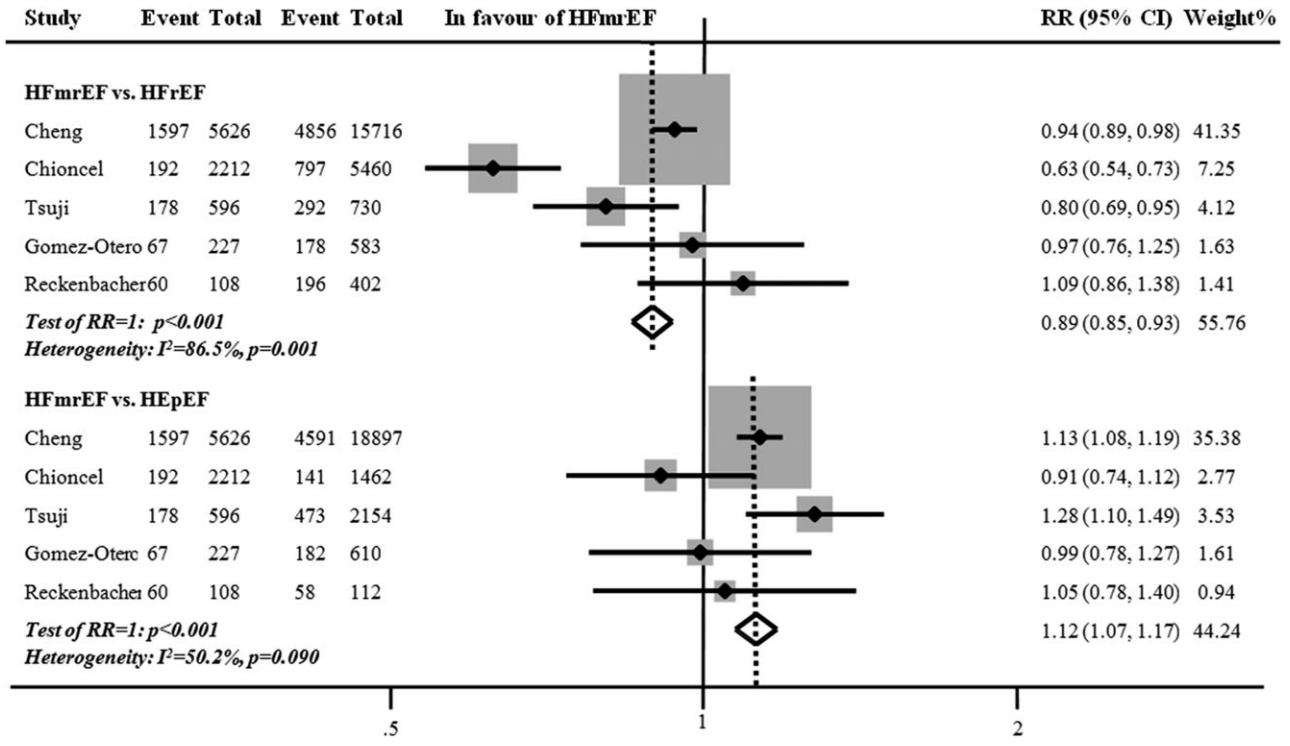


Figure 5 Summary of the study findings illustrating the mid-positioning of heart failure (HF) with mid-range ejection fraction (HFmrEF) between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) concerning the key baseline characteristics. AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease.

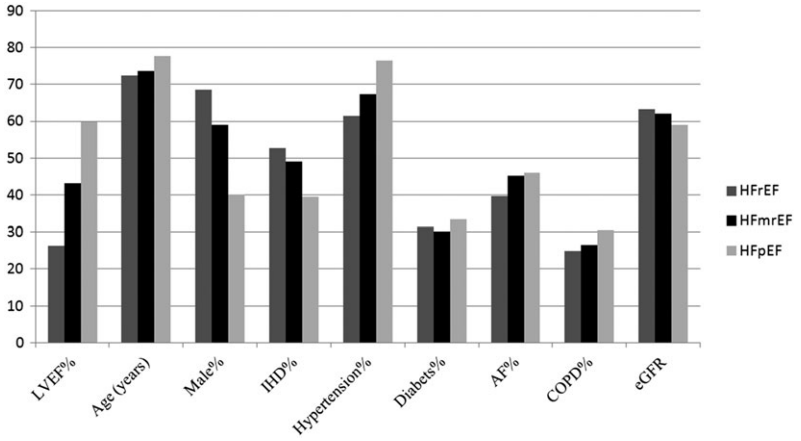
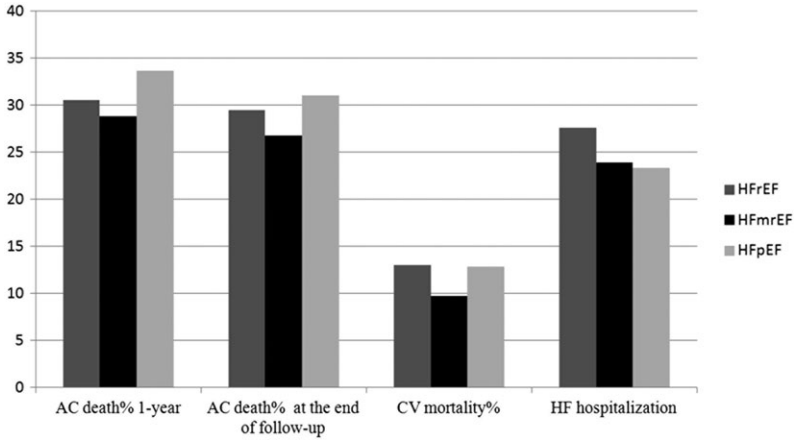


Figure 6 Summary of the study findings illustrating the mid-positioning of heart failure (HF) with mid-range ejection fraction (HFmrEF) between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) concerning the lower all-cause (AC) mortality at 1 year and at the end of follow-up (mean 31 months), cardiovascular (CV) mortality, and HF hospitalization.



Discussion

Including recently published studies with substantial numbers of patients in each CHF category, the results of this meta-analysis demonstrated marked differences in key baseline characteristics, all-cause and cardiovascular mortality, and HF hospitalization between the three categories. Patients with HFmrEF were older, less often male, and less frequently had IHD compared with HFrEF patients. In contrast, HFmrEF patients were younger, more often of male gender, and with IHD compared with HFpEF patients. Baseline co-morbidities such as hypertension, diabetes, and atrial fibrillation were more frequent in patients with HFmrEF than in those with HFrEF but markedly less frequent in patients with HFpEF. Importantly, renal function was worse, and there were more COPD cases among patients with HFpEF than among those with HFmrEF and HFrEF. As expected, use of the recommended medications such as renin–angiotensin system inhibitors and beta-blockers was higher in patients with HFrEF and in those with HFmrEF than in those with HFpEF. All-cause mortality in the first year and after approximately 3 years of follow-up was lowest in HFmrEF. Similarly, cardiovascular mortality was lower in HFmrEF than in both HFrEF and HFpEF patients, while HF hospitalization was markedly lower in HFmrEF than in HFrEF and slightly higher in HFmrEF than in HFpEF. Overall, these epidemiological findings demonstrate that the HFmrEF category occupies an intermediate position between the two established categories concerning clinical profile and burden of co-morbidities, but meanwhile HFmrEF is associated with the lowest mortality. These findings

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strongly support that HFmrEF constitutes a distinct HF category and with distinguished favourable prognosis.

It is well known that IHD is one of the major contributing causes of death in CHF populations.[16,17] The modifying role of IHD in addition to the associated increased use of beta-blockers on LVEF and mortality was well demonstrated in the Swedish registry by Koh *et al*., included in this review.[18] Accordingly, the improved survival and lower HF hospitalizations in the HFmrEF category, as compared with HFrEF, may be explained by the lower prevalence of IHD. Compared with HFpEF, the lower all-cause mortality can be explained by the association of the markedly lower burden of co-morbidities, younger age, and possibly excessive use of beta-blockers and renin–angiotensin system blockers. Most likely, the worse renal function and higher prevalence of COPD contributed considerably to the poorer prognosis of HFpEF patients, despite the lower prevalence of IHD.[19] The role of renal dysfunction as an independent predictor of mortality and the effect of its markedly high prevalence in HFpEF patients have been previously described and currently demonstrated in the Swedish registry.[9] The higher prevalence of IHD and low LVEF in HFrEF and the higher prevalence of hypertension, diabetes, and atrial fibrillation in HFpEF patients may also explain the higher cardiovascular mortality in these two categories as compared with HFmrEF.

Prognosis of CHF patients has been primarily linked with the differences in LVEF as the traditional surrogate of prognosis despite the complex relationship between LVEF and CHF.[20] LVEF has been therefore used as a classification tool to categorize CHF patients. It has been also confirmed that the evidence-based management of these patients, particularly of HFrEF, can reverse the unfavourable remodelling and improve both LVEF and prognosis markedly.[4] Thus, the adverse effect of the remodelling process counteracted by the improving effect of the contemporary therapies has presumably a decisive impact on LVEF dynamics and transition of patients from one into another category.[21] In this context, the suggested concepts of whether HFmrEF constitutes a distinct mid-position phenotype or whether HFmrEF is a transitional phase between HFrEF and HFpEF are worth a debate and further research. In the study by Tsuji *et al*.,[7] the authors examined the dynamic transition between the three CHF categories over 3 years of follow-up and concluded that HFrEF and HFmrEF change categories during follow-up and concluded that HFmrEF represented a transitional status between HFrEF and HFpEF rather than an independent entity. However, a substantial part of HFmrEF patients maintained their position. In contrast, HFpEF seemed to be a more stable category in this study. Lacking similar data from the other included studies on this issue makes it difficult and too early to determine which of the aforementioned concepts is more plausible.

There is increasing evidence that a considerable number of patients with HFrEF recover and improve their LVEF following evidence-based treatment. This group of patients with improved LVEF has been suggested to constitute a distinct category called HF with improved EF (HFiEF).[3] Patients with HFiEF share in fact some key characteristics with HFmrEF patients as they are more often younger females and of non-IHD origin unlike HFrEF patients, and this was pointed out in the study by Junior *et al*.[22] Thus, HFiEF patients, most likely after a category transition, constitute a substantial part of patients with HFmrEF beside those who have been stable and maintained their LVEF between 40% and 50% without deterioration.[23] This LVEF improvement and category change may explain the improved lower all-cause and cardiovascular mortality in patients with HFmrEF compared with patients in the other categories. On the other hand, HFpEF patients whose LVEF deteriorates over time due to developing myocardial infarction or inadequately treated cardiovascular co-morbidities may consequently decline to a lower LVEF category.[21] As a result, it is most likely that HFmrEF is a heterogeneous category comprising patients of different origins with different clinical profiles constituting a mixture of subcategories, who can be classified as HFiEF, HF with stable EF, and HF with worsened EF. However, more pathophysiological research, prospective studies, and retrospective data analyses are needed to consolidate these concepts.

Although LVEF is still considered as an important prognostic surrogate and classification tool of patients with CHF, other well-investigated and relevant parameters have also demonstrated great potential roles characterizing the syndrome of CHF. Circulating biomarkers such as brain natriuretic peptides, echocardiographically measured left atrial size, and myocardial global longitudinal strain and size of myocardial scar tissue measured by magnetic resonance imaging are similarly important prognostic predictors that may guide management of CHF beyond LVEF. Accordingly, new concepts based not solely on LVEF may aid prognosticating and classification of patients with CHF. In future studies, possibly, some of these measures may help to understand the non-linear relation between LVEF and outcome in CHF.

Finally, the important clinical issue beside characterization of HFmrEF patients may be the identification of predictors of deterioration and backward transition to the HFrEF category, in order to prevent further worsening and to improve prognosis. A number of the included studies in the current meta-analysis examined the possible predictors of mortality and effect of the medications used at baseline in patients with HFmrEF.[6,7,10,13,18] There was no consistency in their findings concerning age, gender, atrial fibrillation, or hypertension. Interestingly, subanalyses of the prognostic impact of medications used at baseline showed consistent mortality reduction by beta-blockers in patients with HFmrEF[7,13,18]; however, in the study by Koh *et al*.,[18] this effect was limited to patients with IHD. Because of the presence of IHD and cardiovascular co-morbidities, clinicians do treat HFmrEF patients as HFrEF to some extent, but in the absence of randomized

controlled trials, the evidence is still too weak to treat HFmrEF patients as HFrEF guidelines recommend. It is not unlikely that aldosterone antagonists, beta-blockers, and even prophylactic ICD in subgroups of patients with HFmrEF may improve their survival,[2,24,25] but large-scale randomized controlled trials are required to confirm the beneficial effect of these therapies. Currently, circulating blood biomarkers and various advanced cardiac imaging modalities can certainly also contribute valuable knowledge in this field and may guide treatment.

Limitations

The included studies were of an observational nature, and the investigated populations were heterogeneous concerning the baseline characteristics and the size of prevalence of co-morbidities. Another source of heterogeneity was due to variation in sizes of the included studies, where few larger studies imposed higher impact on the results. Thus, running the mortality and hospitalization analyses in the fixed-effects model was more realistic. The overrepresentation of the HFrEF population, which constituted almost half of the whole analysed population, and the small number of the HFmrEF population may not represent the community-based prevalence of the disease and may be attributed to imbalanced recruitment and registration. Thus, compared with well-treated populations in randomized controlled trials, the mortality estimates may be higher and a time effect is possible. Moreover, some studies did not provide sufficient data for analyses of all baseline characteristics and co-morbidities. This study accounted for the available key baseline characteristics and did not include body mass index, anaemia, stroke, serum brain natriuretic peptide, or HF-related echocardiographic parameters other than LVEF in the analyses. The analysis on HF hospitalization and cardiovascular death as important endpoints may have lacked power because only five studies provided such data. Accordingly, the results of this study should be interpreted cautiously.

Conclusions and perspectives

The results of this study support the notion of HFmrEF as a distinct category that is characterized by a mid-position between HFrEF and HFpEF categories with respect to risk factor profile but is associated with the lowest all-cause and cardiovascular mortality. Despite the superior prognosis, a substantial portion of HFmrEF patients still died of all and cardiovascular causes after approximately 3 years of follow-up, and the all-cause mortality was only slightly lower than that in patients with HFrEF. These findings should encourage more research on patient characterization, mortality predictors, and effect of HF therapies to improve outcomes of patients with HFmrEF.

Conflict of interest

None declared.

References

1. Hobbs FD, Roalfe AK, Davis RC, Davies MK, Hare R, Midlands Research Practices C. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). *Eur Heart J* 2007; **28**: 1128–1134.
2. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Candesartan in heart failure reduction in mortality I. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**: 3738–3744.
3. Writing Committee M, 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, American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: e240–e327.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members; Document Reviewers. 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 J Heart Fail* 2016; **18**: 891–975.
5. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, Hernandez AF, Butler J, Yancy CW, Fonarow GC. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J* 2014; **168**: 721–730.
6. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, 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.
7. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi

J, Miyata S, Shimokawa H. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 study. *Eur J Heart Fail* 2017; **19**: 1258–1269.
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 statement. *SystRev* 2015; **4**: 1.
9. Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail* 2017; **19**: 1606–1614.
10. Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Darling CE, Goldberg RJ. Magnitude of and prognostic factors associated with 1-year mortality after hospital discharge for acute decompensated heart failure based on ejection fraction findings. *J Am Heart Assoc* 2015; **4**: e002303.
11. Gomez-Otero I, Ferrero-Gregori A, Varela Roman A, Seijas Amigo J, Pascual-Figal DA, Delgado Jimenez J, Alvarez-Garcia J, Fernandez-Aviles F, Worner Diz F, Alonso-Pulpon L, Cinca J, Gonzalez-Juanatey JR, Red Espanola de Insuficiencia Cardiaca r. Mid-range ejection fraction does not permit risk stratification among patients hospitalized for heart failure. *Rev Esp Cardiol* 2017; **70**: 338–346.
12. Margolis G, Khoury S, Ben-Shoshan J, Letourneau-Shesaf S, Flint N, Keren G, Shacham Y. Prognostic implications of mid-range left ventricular ejection fraction on patients presenting with ST-segment elevation myocardial infarction. *Am J Cardiol* 2017; **120**: 186–190.
13. Bonsu KO, Owusu IK, Buabeng KO, Reidpath DD, Kadirvelu A. Clinical characteristics and prognosis of patients admitted for heart failure: a 5-year retrospective study of African patients. *Int J Cardiol* 2017; **238**: 128–135.
14. Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, Vazquez R, Delgado-Jimenez J, Alvarez-Garcia J, Gimeno-Blanes JR, Worner-Diz F, Bardaji A, Alonso-Pulpon L, Gonzalez-Juanatey JR, Cinca J. Mid-range left ventricular ejection fraction: clinical profile and cause of death in ambulatory patients with chronic heart failure. *Int J Cardiol* 2017; **240**: 265–270.
15. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, Pfisterer M, Brunner-La Rocca HP. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *Eur J Heart Fail* 2017; **19**: 1586–1596.
16. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017; **10**: e003875.
17. van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014; **16**: 103–111.
18. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634.
19. Canepa M, Straburzynska-Migaj E, Drozdz J, Fernandez-Vivancos C, Pinilla JMG, Nyolczas N, Temporelli PL, Mebazaa A, Lainscak M, Laroche C, Maggioni AP, Piepoli MF, Coats AJS, Ferrari R, Tavazzi L, Investigators E-HHFL-TR. Characteristics, treatments and 1-year prognosis of hospitalized and ambulatory heart failure patients with chronic obstructive pulmonary disease in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **20**: 100–110.
20. Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. *JACC* 2002; **39**: 1414–1421.
21. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail* 2012; **5**: 720–726.
22. Junior WN, West E, Santos M, Skali H, Groarke JD, Forman DE, Shah E. Heart failure and mid-range ejection fraction: implications of recovered ejection fraction for exercise tolerance and outcomes. *Circ Heart Fail* 2016; **9**: 1–17.
23. Punnoose LR, Givertz MM, Lewis EF, Pratibhu P, Stevenson LW, Desai AS. Heart failure with recovered ejection fraction: a distinct clinical entity. *J Card Fail* 2011; **17**: 527–532.
24. Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, Ayis S. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart* 2017; **104**: 407–415.
25. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, Sramko M, Masci PG, Barison A, McKenna P, Mordi I, Haugaa KH, Leyva F, Rodriguez Capitan J, Satoh H, Nabeta T, Dallaglio PD, Campbell NG, Sabate X, Cequier A. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail* 2017; **5**: 28–38.
26. Delepaul B, Robin G, Delmas C, Moine T, Blanc A, Fournier P, Roger-Rolle A, Domain G, Delon C, Uzan C, Boudjellil R, Carrie D, Roncalli J, Galinier M, Lairez O. Who are patients classified within the new terminology of heart failure from the 2016 ESC guidelines? *ESC Heart Fail* 2017; **4**: 99–104.