Dear Sir.

The recent Guidelines of heart failure (HF) of the European Society of Cardiology (ESC) propose an emerging classification of HF according to left ventricular ejection fraction (LVEF)[1]. Namely, patients with LVEF between 40 and 50% are classified in an intermediate group termed HF with mid-range ejection fraction (HFmrEF). Although the authors acknowledge that this subtle distinction may account for important differences in underlying aetiologies, demographics, co-morbidities and response to therapies[2], the group, as a whole, is suggested as a mild systolic dysfunction with features of diastolic dysfunction (sic).

Although a matter of debate[3,4] recent studies offer a view of HF with preserved EF (HFpEF) as a distinct entity of HF with reduced EF (HFrEF). Moreover, it has been proposed that the former is primarily a generalised endothelial dysfunction leading to abnormalities in diastolic properties of the heart[5-7] while the latter is a primarily cardiac disease that impairs both systolic and diastolic function of the heart[6]. Paulus et al[8], suggested that inflammatory mechanisms driven by comorbidities are the key factor leading to, among other, a deficient phosphorylation of titin, responsible for diastolic dysfunction in HFpEF. If this interpretation is correct, comorbidities associated to patients with HFmrEF may have a crucial role in the eventual progression to HF with systolic or diastolic dysfunction.

We aimed to establish the profile of associated comorbidities using the new EF based classification, in a cohort of HF patients consecutively admitted for an acute decompensation of HF.

From February 2013 to July 2014, 204 consecutive patients with worsening heart failure were prospectively enrolled at a tertiary hospital. Eligible patients were at least 18 years of age, hospitalised for worsening heart failure and had an NT-proBNP >300 pg/ml. **All patients had been performed an 2D echocardiography in stable condition during admission or before one month after discharge, unless they had one such test in the three months before current admission.** All patients provided written informed consent. The study was approved by the Ethics Committee (CEICA; CI PI13 / 0019), and supported by a grant from the Ministry of Health (PI12/00694). Statistical analysis. Baseline categorical data were reported as percentages. Continuous variables were summarised as median (and interquartile range). Statistical comparisons between subject groups were performed using the chi-square or Fisher's

exact test for categorical data. For continuous data, the student's t-test or Mann-Whitney U or ANOVA were used for parametric and non-parametric data respectively. A probability value of <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 22.0 (Armonk, NY: IBM Corp).

Two hundred and four patients were included in the study. Their median age was 81±9 years, 51% were men and the median hospital stay was 8 (IQR 7 to 14) days. The most frequent cause for heart failure was hypertension (39%) followed by IHD (29%) and valve disease (mitral and aortic, 9% and 7% respectively). Baseline NYHA functional class, prior to the current admission, was II or III in 172 (84%) patients. One hundred and sixteen patients (57%) had a left ventricular ejection fraction (LVEF) >50%. Prior to admission, 93% of patients were on loop diuretics, 77% on angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB), 56% on beta-blockers, 34% on mineral receptor antagonists and 64% were receiving anticoagulants.

Main characteristics of patients according to EF categories are shown in Table 1. Patients with HFpEF were older, predominantly female, had lower concentrations of the aminoterminal fragment of brain natriuretic peptide (NT-proBNP) and lower creatinine levels prior to admission. Mid-range EF patients showed an intermediate profile, **even for outcomes,** as compared to the other two groups**.** Moreover, the frequency of the comorbidities, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD) and atrial fibrillation were significantly different among groups. Face to face comparison between HFmrEF and HF with reduced or preserved EF yielded further interesting data. The prevalence of both IHD (58.3 vs. 28.6%; p 0.001) and COPD (33.3 vs. 11.4%; p 0.003) were significantly higher in the HFmrEF group as compared to HFpEF, but were not significantly different to those observed in HFrEF patients **(Table 1)**.

According to these results, HFmrEF patients from "real-life" show an intermediate clinical**,** biochemical and **prognostic** profile as compared to those of reduced and preserved EF, being the proportion of the associated comorbidities significantly different. Whether the observed prevalence of comorbidities may be a causal or random association is not known at present time. Not surprisingly, IHD is the main cause of HFrEF and COPD has been proposed as one of the comorbidities leading to HFpEF by eliciting inflammatory mechanisms[8]. **Recent epidemiologic studies have found that comorbidities clusters differently than expected in HF with either preserved or reduced EF**[9]. **If these data are**

correct, it may be suggestive that comorbidities are not merely accompanying conditions, rather they associate following complex pathophysiological relationships, leading to non-expected outcomes[10]. In this context, the role of comorbidities in defining the evolutionary path of HFmrEF towards HF with reduced or preserved EF may be crucial.

A better characterization of patients with EF in the "grey zone" will improve our understanding of such a complex syndrome.

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Table 1 revised

Table 1: baseline characteristics according to ejection fraction.

	HFrEF	HFmrEF	HFpEF	p **value***
Number (%)	**49 (24.1)**	**39 (19.3)**	**116 (56.7)**	**0.000**
Age (years)	78.7 (13)	80.7 (9)	81.6 (9)	0.026
Length of stay (days)	8 (6)	8.5 (5)	9 (7)	0.909
Females	11 (12.2)	12 (33.3)	67 (63.2)	0.000
LVEF (%)	32 (9)	46 (6)	64 (10)	0.000
LVMI (g/m^2)	133 (41)	121 (42)	104 (36)	0.001
LA diameter (mm)	48 (11)	46 (11)	47 (12)	0.108
High blood pressure	35 (79.5)	31 (86.1)	92 (87.6)	0.441
Ischaemic heart disease	21 (47.7)	21 (58.3)	30 (28.6) &	0.003
Atrial fibrillation	20 (45.5)	19 (52.8)	71 (67.6)	0.028
Chronic kidney disease	10 (22.7) **	15 (41.7)	25 (23.8) &	0.087
Diabetes mellitus	18 (40.1)	20 (55.6)	40 (38.1)	0.184
Chronic obstructive pulmonary disease	12 (27.3)	12 (33.3)	12 (11.4) &	0.005
NT-proBNP (pg/mL)	6.073 (8.019)	4.712 (6.317)	2.793 (3.677)	0.000
Cystatin (mg/dL)	1.45 (0.4)	1.55 (0.8)	1.43 (0.8)	0.611
CA125 (mU/L)	74 (87)	57 (61)	51 (88)	0.211
Haemoglobin (g/dL)	12.5 (2.8)	11.6 (3.6)	12.1 (2.7)	0.171
RDW	16.3 (22)	16.2 (4)	15.4 (2.8)	0.122
Uric acid (mg/dL)	8.2 (3.5)	8.1 (3.7)	7.4 (2.4)	0.152
Urea (mg/dL)	55 (3)	59 (3)	55 (4)	0.932
Creatinine (mg/dL)	1.2 (0.3)	1.3 (0.6)	1 (0.6)	0.138
Albumin (g/dL)	3.2 (0.4)	3.3 (0.4)	3.2 (0.6)	0.769
Total cholesterol (mg/dL)	137 (39)	139 (47)	141 (42)	0.385
GGT (UI/mL)	61 (106)	44 (71)	36 (51)	0.001
Sodium (mEq/L)	142 (4)	143 (4)	142 (4)	0.644
Potassium (mEq/L)	4 (0.7)	4.2 (0.5)	4 (0.8)	0.126
HF Admissions (one year follow up)	**24 (54.5)**	**15 (42.9)**	**40 (38.8)**	**0.212**
All-cause Mortality (one year follow up)	**14 (31.1)**	**9 (25.0)**	**20 (18.9)**	**0.250**

Qualitative variables are expressed as absolute number and percentage, quantitative variables as median and interquartile range.

CA 125: **Carbohydrate antigen 125; GGT: Gamma glutamyl transpeptidase;** LA: left atria; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; NT-proBNP: aminoterminal fragment of brain natriuretic peptide; **RDW: Range distribution width**.

*** p value across groups**
**** p value < 0.05 between HFrEF and HFmrEF**
& p value < 0.05 between HFpEF and HFmrEF

***Conflict of Interest Statement**

The authors declare not conflict of interest with regard to this manuscript