ONLINE FIRST

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

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DOI: 10.5603/CJ.a2020.0059

Article type: Original articles

Submitted: 2020-01-15

Accepted: 2020-02-18

Published online: 2020-04-17

Articles in "Cardiology Journal" are listed in PubMed.

Prevalence and prognostic value of monoclonal gammopathy in heart failure patients with preserved ejection fraction: A prospective study

Running title: **Heart failure and monoclonal gammopathies**

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Abstract

Background: Heart failure (HF) with preserved ejection fraction (HFpEF) and monoclonal gammopathy of uncertain significance (MGUS) are two entities that share pathophysiological mechanisms. The aim herein, was to assess the prevalence of MGUS in patients with HFpEF and no left ventricular (LV) hypertrophy, as well as its association with a pre-specified clinical endpoint at 12 months.

Methods: The present study prospectively enrolled 69 patients admitted with HF, with ejection fraction ≥ 50%, and LV wall thickness < 12 mm. All patients were screened for MGUS. Clinical events were determined over a 12 month follow-up. The pre-specified composite clinical endpoint was readmission for heart failure or death.

Results: The prevalence of MGUS in this population was 13%. There were no differences in the incidence of the composite clinical endpoint between patients with and without MGUS. Multivariate analysis showed that treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was associated with fewer clinical events (HR: 0.153, 95% CI: 0.037–0.622, p = 0.009) and indicated a trend to lower risk of readmission for HF and death. Beta-blockers were associated with lower rates of the composite clinical endpoint (HR: 0.192, 95% CI: 0.05–0.736, p = 0.016), readmission for HF (HR: 0.272, 95% CI: 0.087–0.851, p = 0.025) and indicated a trend to lower mortality. Moreover, potassium serum levels > 5 mEq/L were associated with higher rates of the composite endpoint (HR: 6.074, 95% CI: 1.6–22.65,p = 0.007).

Conclusions: The prevalence of MGUS in patients with HFpEF without hypertrophy was 3-fold that of the general population. There was no significant correlation between clinical outcomes and the presence of MGUS. Beta-blockers and ACEIs/ARBs reduced the composite of mortality and readmissions for HF in HFpEF patients. Hyperpotassemia was related to worse prognosis.

Key words: monoclonal gammopathy, heart failure, inflammation, ACEI, ARB

Introduction

Heart failure (HF) is a clinical syndrome characterized by symptoms and signs. HF is caused by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac pressure at rest or during stress [1]. According to European guidelines [1] patients present HF with preserved ejection fraction (HFpEF) when left ventricular ejection fraction (LVEF) is ≥ 50%, with elevated levels of natriuretic peptides (B-type natriuretic peptide [BNP] > 100 pg/mL and/or N-terminal pro-BNP [NT-proBNP] > 300 pg/mL in the acute setting) and at least one additional criterion, such as relevant structural heart disease (left ventricular hypertrophy [LVH] and/or left atrial enlargement) or diastolic dysfunction. Recent diagnostic algorithms suggest some functional, morphological and biomarker-related criteria for a more accurate diagnosis of HFpEF [2].

Heart failure affects ≥ 10% of > 70-year old population and up to 50% of all cases of HF are believed to be caused by HFpEF [1, 3–5]. Its prevalence has been increasing in recent decades, related to the higher percentage of elderly individuals in the population. However, epidemiological data are difficult to acquire. One meta-analysis found a mortality rate of 12.1% during the first year [6]. A new pathophysiological model for HFpEF has been recently suggested [5], explaining it as an inflammatory disease. Typically, HFpEF patients are elderly with several inflammation-related comorbidities (i.e. diabetes, hypertension), which may explain the link between those proinflammatory entities and the presence of HFpEF.

Monoclonal gammopathies (MGs) are a group of entities associated with the proliferation of a single clone of plasma cells. MGs include conditions ranging from monoclonal gammopathy of uncertain significance (MGUS), multiple myeloma (MM), lymphoplasmacytic lymphoma (LL), and primary amyloidosis (AL) [7,8]. Patients with MGUS present monoclonal immunoglobulin concentrations of ≤ 3 g/dL in serum; in the absence of lytic bone lesions, anemia, hypercalcemia, and kidney failure related to the proliferation of monoclonal plasma cells; and ≤ 10% of plasma cells in the bone marrow [7,8]. The prevalence of MGUS is 4.22% among individuals ≥ 60 years of age in the general population [8]. Clinical relevance of MGs lies in their high prevalence and underdiagnosis, but mainly due to the risk of progression to other entities (16% at 10 years) [8]. All the diseases within the MG spectrum may show cardiac involvement, with myocardial deposits of paraprotein or its components, that generate a diastolic alteration leading to a restrictive pattern and HF [9–13]. MGs trigger a proinflammatory state [14] that could contribute to the development of diastolic alterations at a cardiac level.

Both HFpEF and MGUS are increasing in prevalence among the older population. Given the pathogenesis, both may rely on immune system activation and inflammation mechanisms [14, 15], suggesting a possible link between them.

HFpEF has been described in patients without LV hypertrophic remodeling [16] who accomplished other of the definition criteria for HFpEF [1, 2]. Patients with LVH have a high incidence of infiltrative diseases [17]. In this study it was sought to select patients without significant hypertrophy (< 12 mm), thereby with less probability to present with an infiltrative disease and try to establish a correlation between them and the presence of MGUS.

This study sought to determine whether a correlation exists between HFpEF without significant LVH and the presence of MGUS. Based on the epidemiological resemblances and a possible inflammatory process underlying both entities, it was hypothesized that MGUS could be more prevalent in cases of HFpEF than in the general population. Testing the secondary hypothesis, was an inquiry as to whether a correlation exists between the presence of MGUS and the clinical outcomes in HFpEF (composite endpoint of rehospitalization for HF and mortality, and each component of the combined endpoint).

Methods

Study design

This is an observational, prospective, single-center, and prevalence study. Only those patients who provided signed written consent were enrolled. The study was approved by Fundación Jiménez Díaz Ethics Committee.

Study population

Patients were recruited following admission to the Fundación Jiménez Díaz hospital in Madrid. All patients had a diagnosis of HFpEF (see inclusion criteria) at the time of hospitalization. The hospital database updated with patient status, test results, scans, and assessments from all hospital departments. Furthermore, the online health-care database for the entire region of Madrid was searched to determine whether patients had presented to an Emergency Department or other service and the exact date of death in cases where the patient died.

Inclusion criteria

Inclusion criteria included:

— age ≥18 years;

— clinical signs and/or symptoms typical of HF (such as rales and crackles at auscultation, pulmonary congestion as seen through chest X-rays, third heart sound), BNP > 100 pg/mL or NT-proBNP > 300 pg/mL at hospitalization, in full accordance with current guidelines [1];

— LVEF ≥ 50% at hospitalization (evidenced in a recent echocardiogram at point of care or *in loco*);

— LV wall thickness < 12 mm at thickest point (recent echocardiogram at point of care or *in loco*).

Exclusion criteria

All patients that met any of the criteria below were excluded from the study:

— pre-existing heart condition that may explain HF (i.e. moderate to severe valvular disease, prosthetic valve, severe anemia or hyperdynamic circulation, advanced second- or third-degree atrioventricular block proven by a pathologic electrocardiogram track, etc.);

— substantial or severe comorbidity that, according to the enroller's judgement, would indicate deteriorated cardiac function;

— previous or known diagnosis of multiple myeloma, amyloidosis, or lymphoplasmacytic lymphoma;

— autoinflammatory disease or infection that could explain MG.

Enrollment, physical examination, laboratory tests, and imaging

Patients who met all inclusion and none of the exclusion criteria provided a written statement of consent, in accordance with the requirements of the local ethics committee and in adherence of Spanish law.

Upon enrollment, all patients underwent a whole-body physical examination and the following laboratory tests were performed: complete blood count, basic biochemical markers, serum proteins, protein electrophoresis test, immunofixation electrophoresis (serum and urine) and light chains (serum and urine). As mentioned in inclusion criteria, one of the criteria for the diagnosis of HF was BNP > 100 pg/mL or NT-proBNP > 300 pg/mL at hospitalization [1]. Moreover, another variable was created, "Elevated natriuretic peptides", that was defined as levels of BNP or NT-proBNP greater than or equal to the median (BNP > 368 pg/mL or NT-proBNP > 1900 pg/mL). Demographic data, cardiovascular risk factors, clinical history, echocardiographic parameters and treatments were recorded. Enlarged left atrium (LA) was considered when LA maximum diameter in a parasternal long-axis view was ≥ 35 mm or when LA major length in an apical four-chamber view was ≥ 53 mm [18]. Diastolic function was classified as normal diastolic function, indeterminate or diastolic dysfunction [19].

When a monoclonal component was found, patients were referred to the Hematology Department, where they underwent a complete evaluation and risk stratification. MGUS was defined as present monoclonal immunoglobulin concentrations of ≤ 3 g/dL in serum, in the absence of lytic bone lesions, anemia, hypercalcemia, and kidney failure related to the proliferation of monoclonal plasma cells; and ≤ 10% of plasma cells in the bone marrow [7, 8].

At 12 months, the electronic medical records were reviewed for events (hospitalization for heart failure and mortality).

Data management and processing

Two data sheets were used for data collection and analysis:

— Database #1: Excel spread sheet containing the pairings (Last name, Name, Medical record number), and the *study number* (randomized number, not related to the patient in any way or by its clinical file number, and not generated from the patient's data).

This database was the only one containing the patients' personal data, and it contained no data related to the study or any data related to their health;

— Database #2: The *study number* was paired to all of the data retrieved and gathered from the patient. This database contained sensible information but when consulted alone, patient identification was impossible.

Once the enrollment process was complete, only the second database was used for the purpose of analysis, making the process fully anonymous and non-traceable.

All data were handled and processed in full accordance with local and European law.

Statistical analysis

Quantitative variables are displayed as medians (interquartile range). Qualitative variables appear as percentages.

To predict the endpoint at 12 months, a univariate Cox regression analysis for all variables was performed. Next, a multivariate analysis was carried out to determine whether any of the variables could independently predict major events with the variables with a p value in univariate analysis < 0.2.

The Kaplan-Meier curves and log-rank test were used to compare time to outcome according to those variables significantly associated with a higher risk of developing the primary outcome.

Analyses were performed with SPSS 19.0 (SPSS Inc., New York). Statistical tests in which $p < 0.05$ (two-tailed) were considered significant.

Results

Study population

Two hundred nine patients admitted with HF to the Fundación Jiménez Díaz were preselected between July 17, 2017 and November 11, 2018. One hundred thirty-eight patients

were excluded (Fig. 1). Two patients were excluded of the analyses because they didn´t undergo blood tests. The final number of patients analyzed was sixty-nine.

Statement of Ethics

Only patients that signed written consent for the study were enrolled. The study was approved by Fundación Jiménez Díaz Ethical Committee.

Baseline characteristics

The mean age was 83 years, with 46.4% males (Table 1). Atrial fibrillation was present in 63.8%. Other cardiovascular risk factors that can indicate underlying inflammatory mechanisms were very frequently present, such as diabetes (30.4%), dyslipidemia (56.5%) and hypertension (81.2%). Most patients were under loop diuretics (73.9%) and 50.7% were receiving angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Median BNP was 368 pg/mL and median NT-proBNP was 1900 pg/mL. Natriuretic peptides were elevated over the median (BNP > 368 pg/mL, NT-proBNP > 1900 pg/mL) in 59.6% of patients. Potassium levels were higher than 5 mEq/L at admission in 10.1% of the patients. Characteristics by groups (combined endpoint, rehospitalization for heart failure and mortality) are presented in Table 1A, B.

Prevalence of MGUS in the HFpEF patient cohort

The prevalence of MGUS among the patients with HFpEF and LV wall thickness < 12 mm, was 13% (n = 9) (Table 1A). There were no significant differences in the number of patients with or without MGUS by group (Table 1A, B).

Eight patients had a low risk MGUS and did not need any other complementary test; a follow-up was programmed by the Hematology Department in these patients. 1 patient did not enter into the study because of death.

Clinical events (combined endpoint, hospitalization for HF, mortality)

At 12-month follow-up, 34 (49.2%) patients had met the composite endpoint of mortality or rehospitalization for HF. 18 (26%) patients had been readmitted for HF at least once and 11 (16%) patients had died (Table 1A, B). In the group with diagnosis of MGUS, 2 (22%) of patients met the composite clinical endpoint, 1 (11.1%) patient was readmitted for HF and 1 (11.1%) patient died; versus 22 (37.5%), 17 (28.3%) and 10 (16.7%), respectively in the group without MGUS (Table 2).

Factors influencing the outcome

The single variable Cox regression was performed for each category of data with regard to the composite endpoint, readmission for HF and mortality. A multivariate Cox analysis showed that patients taking ACEIs/ARBs were less likely to present the combined clinical endpoint (hazard ratio [HR]: 0.153, 95% confidence interval [CI]: 0.037–0.622, p = 0.009), and had a trend to lower risk of readmission for HF (HR: 0.353, 95% CI: 0.121–1.026, p = 0.056) and mortality (HR: 0.275, 95% CI: 0.073–1.041, p = 0.057; Table 3A–C). Moreover, patients taking beta-blockers were also less likely to present the combined clinical endpoint (HR: 0.192, 95% CI 0.05–0.736, p = 0.016), to be readmitted for HF (HR: 0.272, 95% CI: 0.087–0.851, p = 0.025) and had a trend to lower risk of death (HR: 0.27, 95% CI: 0.058–1.249, p = 0.094; Table 3A–C). Besides, patients with potassium serum levels > 5 mEq/L at admission were more likely to present the combined clinical endpoint (HR: 6.074, 95% CI: 1.6–22.65, p = 0.007; Table 3A). Patients taking clopidogrel had higher risk of being readmitted for HF (HR: 7.938, 95% CI: 1.458–43.227, p = 0.017; Table 3B).

The Kaplan-Meier curves showed that taking betablockers resulted in lower rates of the combined clinical endpoint and readmission for HF, with a trend to lower mortality (Fig. 2A–C). ARBs/ACEIs were protective in terms of the combined clinical endpoint and had a trend to decreased rehospitalization for HF (Fig. 3A, B). Moreover, patients with potassium serum levels > 5 mEq/L at admission were more likely to present the combined endpoint when compared to those with lower potassium levels (Fig. 4).

Discussion

The prevalence of MGUS in patients with HFpEF and LV wall thickness < 12 mm was 3 times higher than that in the general population (13% vs. 4.22%). It can therefore be deduced that patients with MGUS should be assessed for HF symptoms. In future, MGUS may be incorporated into a diagnostic work-up that may include cardiac damage markers, or echocardiography [20, 21].

For the clinical endpoints, rates of readmission for HF at 12 months was 26%, which is lower than previously described, which might be related to the fact that previous studies usually include both patients with reduced and preserved ejection fraction [22]. The mortality rate of these patients was 16% at 1 year, which was slightly higher than in previous studies [22].

A correlation between outcomes and presence or absence of MGUS could not be demonstrated. Since there is no direct proof of cardiotoxicity in MGUS, MGUS may be an initial phase (as a first laboratory sign) of protein deposit disease, such as amyloidosis, or even progress into multiple myeloma. Even though amyloidosis would drastically change the outcome of any patients in the sample presenting the disease, patients were specifically selected that had an LV wall thickness < 12 mm, possibly excluding most of the amyloid patients, which usually present with LVH. Moreover, the follow-up period in this study was far too short for these entities to manifest and consequently alter the outcome of MGUS patients.

ACEIs/ARBs were related to better outcomes in terms of the combined endpoint and had a trend to lower rates of readmission for HF and mortality at 12 months. Though patients were not categorized by the New York Heart Association/American Heart Association functional class, it was deduced from these results that HFpEF patients might benefit from ACEIs/ARBs as this therapy approach would downgrade their risk stratum. These results are encouraging, especially considering that the most promising drug, sacubitril/valsartan showed no benefit when compared to valsartan in the PARAGON-HF, in HFpEF [23]. The use of ACEIs/ARB in HFpEF has been previously suggested in a recent meta-analysis [24], although single large studies failed to demonstrate this relation [25, 26].

The mechanism behind the seemingly protective action of ACEIs/ARBs remains unclear, but it may have to do with the pathophysiological mechanism of HF itself. Hypertension and cardiac remodeling play a role in the pathogenesis; moreover, the renin–

angiotensin–aldosterone axis is closely related to inflammation and its byproducts. This would justify the rationale behind such an effect, as well as the synergy. The benefits shown at short follow-up (Fig. 3A, B) draws attention to the shorter-acting mechanism of cardio-protection.

Beta-blockers showed a clear benefit in terms of the combined clinical endpoint, and in terms of readmission for heart failure, with a trend to a lower mortality. Previous studies in HFpEF patients did not show any significant effect of beta-blockers [27, 28]. However, hypotheses have been made about the mechanism of betablockers in HFpEF. Subendocardial ischemia is one of the mechanisms that has been suggested in the physiopathology of HFpEF. Beta-blockers may improve diastolic filling, enhancing relaxation, and decreasing subendocardial ischemia. Other mechanisms such as control of precipitant factors (hypertension, tachyarrhythmia) have been suggested for the role of betablockade in HFpEF.

HFpEF population is very heterogeneous; it affects elderly patients with several comorbidities (i.e. diabetes, hypertension) and different cardiac phenotypes (i.e. hypertrophic cardiomyopathy, infiltrative disease, hypertensive cardiomyopathy). Moreover, the definition of HFpEF has changed over the time, and the current European guidelines [1] define HFpEF when LVEF ≥ 50%, and HF with mid-range ejection fraction when LVEF is 40–49%. Some large studies have included a very heterogeneous profile of patients; for example, PARAGON-HF [23], included patients with LVEF ≥ 45% and any wall thickness, and failed to show any benefit from sacubitril/valsartan in comparison with valsartan. One explanation could be that the population selected presented with different entities in the spectrum of HFpEF, and the pathophysiological mechanisms and the response to therapies might have been different in each form.

In the present study, a very selected population of patients fulfilling criteria for HFpEF were included, with an LVEF ≥ 50% and with a maximal LV wall thickness of < 12 mm. In these concrete populations, the response to ACEI, ARB and beta-blockers was beneficial. The present hypothesis is that each form of HFpEF has a different profile, and a narrower approach to each entity integrating the big group of HFpEF could be useful for identifying the optimal therapy.

Interestingly, it was found that high potassium levels at entry (defined as k > 5 mEq/L) was a negative prognostic factor for outcome, in terms of higher readmission for HF and mortality rates. The explanation for this may be that, on the one hand, hyperpotassemia may

indicate that the patient is not receiving enough non-potassium-sparing diuretics; and on the other hand, it can also reflect a certain degree of kidney failure and has been previously associated with increases in cardiovascular and HF-related events [29].

On the other hand, patients taking clopidogrel had a higher risk of being readmitted for HF, which might be explained by more coronary artery disease and vascular disease, which might increase risk for these patients.

This study has some limitations that may explain the failure to show a correlation between the presence of MGUS and clinical outcomes in HFpEF patients. In the first place, this is an observational and unicentric study, with possible selection bias that this study design implies and the limitation to extrapolate data to the general population. Second, sample size (n = 69) was not large and may have limited the ability to establish a relationship between HFpEF and MGUS. However, the findings reported herein may serve as a proof-of-concept, suggesting a need to search for MGUS in patients with HFpEF. Third, longer follow-up periods and larger studies are needed to truly assess the impact of MGUS on survival and hospitalization for HF.

Conclusions

In conclusion, the prevalence of MGUS in HFpEF patients with no LVH was roughly three-fold that of an age-matched general population; thus, it may be suggested that patients with MGUS be assessed for possible HF. Though a correlation was not found between MGUS and clinical outcomes for this population of HFpEF patients, longer follow-up studies are needed to fully rule out this possibility. The use of betablockers and ACEI or ARB reduced the combined endpoint of mortality and rehospitalization for HF in this HFpEF population, which may support the use of these treatments of these patients. Higher potassium levels may be a marker of poor prognosis in this population, and closer follow-up should be considered. Further studies are needed to clarify the state-of-the-art therapy for these patients, as their prevalence increases.

Acknowledgements

We acknowledge Oliver Shaw (Instituto de Investigación sanitaria (IIS) - Fundación Jiménez Díaz, Madrid, Spain) for his assistance in editing this article.

Funding: This work was supported by grants from Instituto de Salut Carlos III (PI19/00655), financed jointly with European Regional Development Funds (ERDF).

Conflict of interest: None declared

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Table 1A. Basal characteristics (total population and combined endpoint of mortality and readmission for heart failure).

Population description	**Total (n = 69)**	**No combined endpoint (n = 35)**	**Combined endpoint (n = 34)**	**P**
Age [years]	83 (77–86)	82 (77–87)	83 (79–86)	0.605
Males	46.4	51.1	37.5	0.282
Diabetic	30.4	31.1	29.2	0.867
Smokers	32.4	31.8	33.3	0.898
Dyslipidemia	56.5	60	50	0.426
Arterial hypertension	81.2	84.4	75	0.343
Atrial fibrillation	63.8	62.2	66.7	0.715
Ischemic heart disease	14.5	15.6	12.5	0.732
MGUS	13	15.6	8.3	0.403
Medication at day 1				
ASA	24.6	24.4	25	0.959
Anticoagulation	63.8	64.4	62.5	0.873
Clopidogrel	4.4	2.2	8.3	0.276
ACEIs or ARBs	50.7	60	33.3	0.038
Beta-blockers	43.5	53.3	25	0.027
CCB	17.4	15.6	20.8	0.583
Thiazide diuretics	18.8	13.3	29.2	0.117
Loop diuretics	73.9	75.6	70.8	0.427
MRA	14.5	8.9	25	0.081

Digoxin	8.7	6.7	12.5	0.420
Statins	52.2	57.8	41.7	0.204
Antiarrhythmics	7.2	6.7	8.3	0.8
Laboratory values				
Albumin levels [g/dL]	4.00 (3.75–4)	4.00 (3.5–4)	4.00 (4–4)	1
Total protein count [g/dL]	6.5 (6–7.07)	6.7 (6.1–7.125)	6.3 (5.7–7.07)	0.370
Creatinine [mg/dL]	1.1 (0.8–1.377)	1.1 (0.8–1.33)	1.08 (0.8–1.57)	0.446
eGFR [mL/min]	56.9 (46.4–74)	57 (48–77.9)	56.4 (37.5–68.1)	0.205
Glycaemia [mg/dL]	104 (88.5– 27)	105 (92–123)	101 (86.5–141)	0.855
Hemoglobin [g/dL]	12.2 (11.1–13.15)	12.2 (11.3–13)	11.9 (10.9–13.5)	0.806
Platelet count [n/mm^3]	208 000 (174000–279500)	215000 (174000–290500)	192000 (171250–242250)	0.453
WBC count [n/mm^3]	6930 (5770–8975)	7000 (6000–9150)	6425 (5700–8395)	0.326
Segmented neutrophils [%]	67.5 (61.7–74)	67 (61–74)	67.9 (62–81)	0.469
Sodium [mEq/L]	139 (136–141)	139 (136–142)	139 (135–141)	0.519
Potassium [mEq/L]	4.2 (3.8–4.55)	4.2 (3.7–4.3)	4.2 (4–4.7)	0.225
NT-proBNP [pg/mL]	1900 (1096–2960)	1600 (894–2628)	3140 (2200–9990)	0.121
BNP [pg/mL]	368 (130–885)	218 (112–495)	595 (400.5–1128)	0.003
Potassium > 5 mEq/L	10.1	4.4	20.8	0.049
Natriuretic peptides over the median†	59.6	51.2	81.3	0.047
Echocardiographic values				
Ejection fraction	60 (55–60)	60 (55–60)	60 (51–63.7)	0.742
LA (PLA) [mm]	41 (36–45)	41 (37–45)	41 (36–45)	0.354
LA (AFC) [mm]	59 (53–63.5)	59 (55–63)	58 (50–65)	0.414

LA dilatation	88.4	86.7	91.7	0.54
Diastolic dysfunction or non-evaluable	98.6	97.3	100	0.282

Values are median (interquartile range) or percentages. †Natriuretic peptides over the median were defined as NT-proBNP levels > 1900 pg/mL or BNP > 368 pg/mL.

ACEIs — angiotensin converter enzyme inhibitors; AFC — apical four chamber; ARBs — angiotensin II receptor blockers; ASA — acetylsalicylic acid; BNP — B-type natriuretic peptide; CCB — calcium channel blockers; eGFR — estimated glomerular filtration rate; LA — left atrium; MGUS — monoclonal gammopathy uncertain significance; MRA — mineral corticoid receptor antagonists; NT-proBNP — N-terminal pro-BNP; PLA —parasternal long axis; WBC — white blood cell

Table 1B. Basal characteristics (readmission for heart failure [HF] and mortality).

Population description	**Readmission for HF (n = 18)**	**No readmission for HF (n = 51)**	**P**	**Mortality (n = 11)**	**No mortality (n = 58)**	**P**
Age [years]	83.5 (81.8–87.2)	81 (77–86)	0.108	82 (77–86)	83 (77–87)	0.693
Males	33.3	51	0.201	36.4	48.3	0.470
Diabetic	27.8	31.4	0.776	18.2	32.8	0.344
Smokers	27.8	33.3	0.629	36.4	31	0.756
Dyslipidemia	44.4	60.8	0.233	54.5	56.9	0.885
Arterial hypertension	77.8	82.4	0.670	63.6	84.5	0.117
Atrial fibrillation	72.2	60.8	0.388	54.5	65.5	0.49
Ischemic heart disease	5.6	17.6	0.237	18.2	13.8	0.706
MGUS	5.6	15.7	0.295	9.1	13.8	0.674
Medication at day 1						
ASA	16.7	27.5	0.366	27.3	24.1	0.825
Anticoagulation	72.2	60.8	0.388	54.5	65.5	0.490
Clopidogrel	11.1	2	0.15	9.1	3.4	0.426
ACEIs or ARBs	38.9	54.9	0.246	27.3	55.2	0.102

Beta-blockers	22.2	51	0.041	18.2	48.3	0.082
CCB	22.2	15.7	0.531	9.1	19	0.440
Thiazide diuretics	22.2	17.6	0.67	36.4	15.5	0.117
Loop diuretics	66.7	76.5	0.275	81.8	72.4	0.691
MRA	22.2	11.8	0.286	27.3	12.1	0.202
Digoxin	16.7	5.9	0.18	0	10.3	0.999
Statins	38.9	56.9	0.194	45.5	53.4	0.627
Antiarrhythmics	11.1	5.9	0.469	0	8.6	0.999
Laboratory values						
Albumin levels [g/dL]	4 (4–4)	4.00 (3.5–4)	1	4 (4–4)	4 (3.75–4)	1
Total protein count [g/dL]	6.3 (5.6–7)	6.7 (6.1–7.2)	0.220	6.4 (5.7–7.7)	6.5 (6.05–6.9)	0.908
Creatinine [mg/dL]	1.05 (0.8–1.32)	1.1 (0.8–1.37)	0.967	1.19 (0.8–1.7)	1.07 (0.8–1.3)	0.321
eGFR [mL/min]	56.9 (47–68.1)	56.9 (45–76)	0.481	51 (37–68.1)	57 (48–74.5)	0.235
Glycaemia [mg/dL]	95 (82.2–143)	107 (92–124)	0.280	97 (80–122)	104.5(91.7–130.2)	0.354
Hemoglobin [g/dL]	11.8(10.9– 3.6)	12.2 (11.2–13.1)	0.722	11. (10.9–14)	12.2(11.2–13.1)	0.426
Platelet count [n/mm^3]	192000 (168500–8750)	215000 (173000–296000)	0.328	185000 (170000–246000)	213500 (174500–282750)	0.566
WBC count [n/mm^3]	6425 (4955–7945)	7000 (5960–9410)	0.176	5900 (5740–9690)	7000 (5917–8962)	0.363
Segmented neutrophils [%]	67.9 (60.5–84.3)	67 (62–73)	0.448	67.1 (61.3–73)	67.9 (61.8–75.5)	0.87
Sodium [mEq/L]	139.5 (136–141)	139 (136–141)	0.896	137 (135–140)	136 (139–141)	0.361
Potassium [mEq/L]	4.3 (3.9– 4.9)	4.2 (3.7–4.3)	0.166	4.2 (4–4.6)	4.1 (3.7–4.5)	0.616

NT-proBNP [pg/mL]	2350 (1271–2980)	1900 (1074–3310)	0.748	6915 (1681.5–22897.5)	1900 (1074–2635)	0.113
BNP [pg/mL]	595 (292–1000)	262 (1129–730)	0.147	522.5(338–1464.5)	281.5 (129.75–781.75)	0.197
Potassium > 5 mEq/L	22.2	5.9	0.064	9.1	10.3	0.9
Natriuretic peptides over the median†	75	55.6	0.231	71.4	58	0.5
Echocardiographic values						
Ejection fraction	60 (58.5–60)	60 (55–60)	0.305	60 (50–65)	60 (55–60)	0.993
LA (PLA) [mm]	41.5 (36–46.7)	41 (36.2–44.7)	0.64	38(33–42.5)	42 (37–45.5)	0.207
LA (AFC) [mm]	59 (50.7–69.5)	59 (54–62)	0.633	57 (50–60)	60 (54.7–65)	0.083
Left atrium dilatation	94.4	86.3	0.369	81.8	89.7	0.463
Diastolic dysfunction or non-evaluable	100	98	0.355	100	98.3	0.205

Values are median (interquartile range) or percentages. †Natriuretic peptides over the median were defined as NT-proBNP levels > 1900 pg/mL or BNP > 368 pg/mL.

ACEIs — angiotensin converter enzyme inhibitors; AFC — apical four chamber; ARBs — angiotensin II receptor blockers; ASA — acetylsalicylic acid; BNP — B-type natriuretic peptide; CCB — calcium channel blockers; eGFR — estimated glomerular filtration rate; LA — left atrium; MGUS — monoclonal gammopathy uncertain significance; MRA — mineral corticoid receptor antagonists; NT-proBNP — N-terminal pro-BNP; PLA —parasternal long axis; WBC — white blood cell

Table 2. Outcomes by group (presence or absence monoclonal gammopathy of uncertain significance [MGUS])

	MGUS (n = 9)	**No MGUS (n = 60)**	**P**
Composite endpoint	2 (22.2%)	22 (36.7%)	0.403
Admission for HF	1 (11.1%)	17 (28.3%)	0.295

Mortality	1 (11.1%)	10 (16.7%)	0.674

Values are number of patients and percentages. HF — heart failure

Table 3A. Multivariate Cox regression for combined endpoint (admission for heart failure and mortality)

Variable	Hazard ratio	95% confidence interval	P (multivariate)
ACEIs or ARBs	0.153	0.037–0.622	0.009
Beta-blockers	0.192	0.05–0.736	0.016
Potassium > 5 mEq/L	6.074	1.6–22.65	0.007

ACEIs — angiotensin converter enzyme inhibitors; ARBs — angiotensin II receptor blockers

Table 3B. Multivariate Cox regression for admission for heart failure.

Variable	Hazard ratio	95% confidence interval	P (multivariate)
ACEIs or ARBs	0.353	0.121–1.026	0.056
Beta-blockers	0.272	0.087–0.851	0.025
Clopidogrel	7.938	1.458–43.227	0.017

ACEIs — angiotensin converter enzyme inhibitors; ARBs — angiotensin II receptor blockers

Table 3C. Uni- and multivariate Cox regression for admission for mortality.

Variable	Hazard ratio	95% confidence interval	P (multivariate)
ACEIs or ARBs	0.275	0.073–1.041	0.057
Beta-blockers	0.27	0.058–1.249	0.094

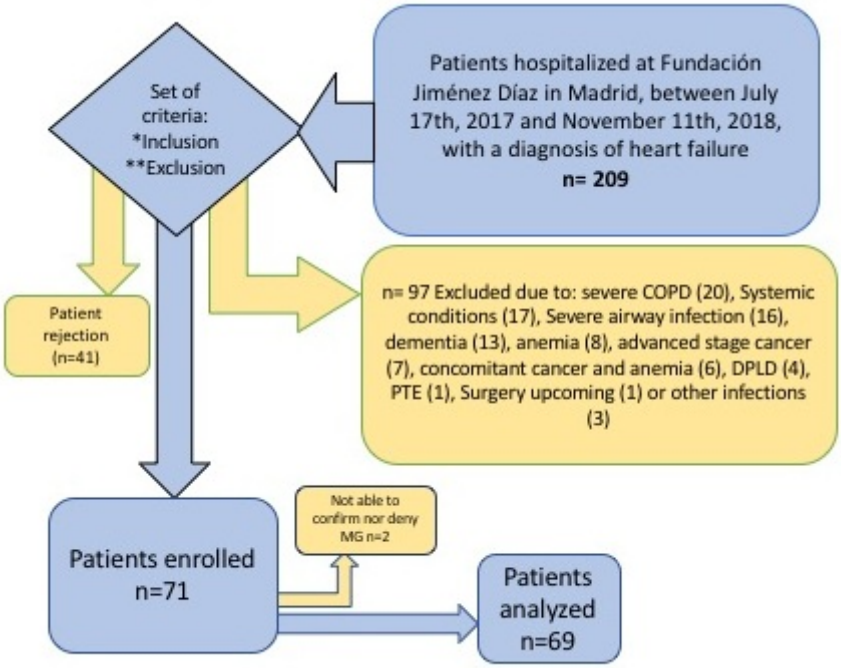
ACEIs — angiotensin converter enzyme inhibitors; ARBs — angiotensin II receptor blockers

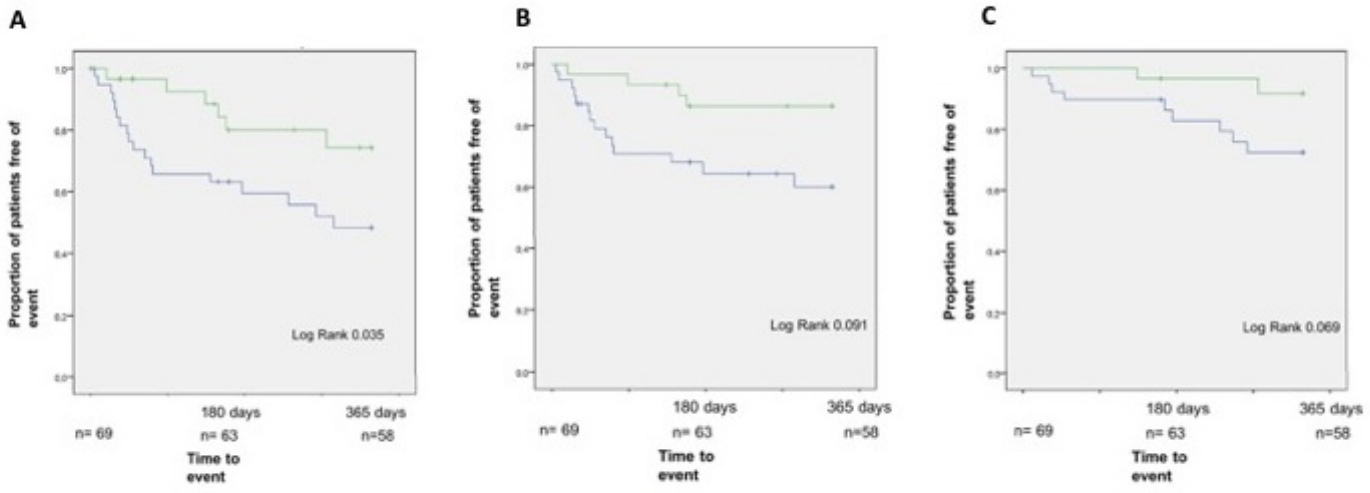
Figure 1. The recruiting and enrollment process; COPD — chronic obstructive pulmonary disease; DPLD — diffuse parenchymal lung disease; PTE — pulmonary thromboembolism.

Figure 2. Kaplan-Meier curves comparing patients taking beta-blockers with patients not taking beta-blockers; **A.** Time to composite endpoint; **B.** Time to rehospitalization for heart failure; **C.** Time to death.

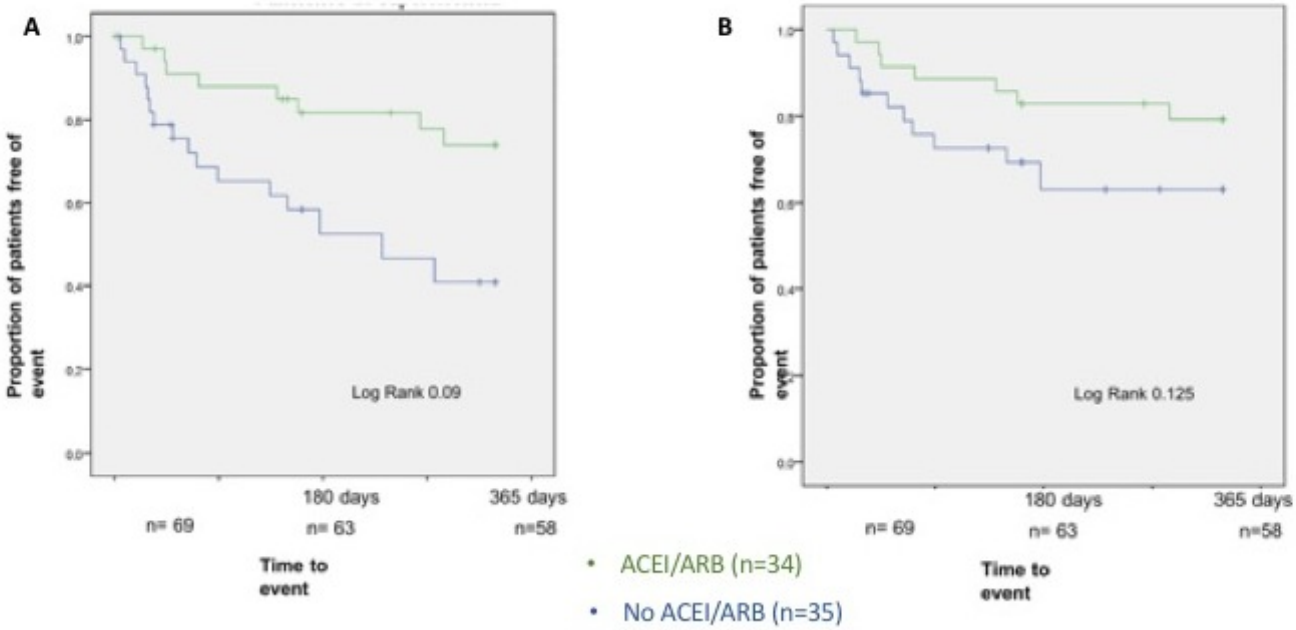
Figure 3. Kaplan Meier curves comparing patients taking angiotensin converter enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) with patients not taking ACEI/ARB; **A.** Time to composite endpoint; **B.** Time to re-hospitalization for heart failure.

Figure 4. Kaplan-Meier curves comparing patients with potassium levels > 5 mEq/L with patients with potassium levels < 5 mEq/L by the time to the composite clinical endpoint.

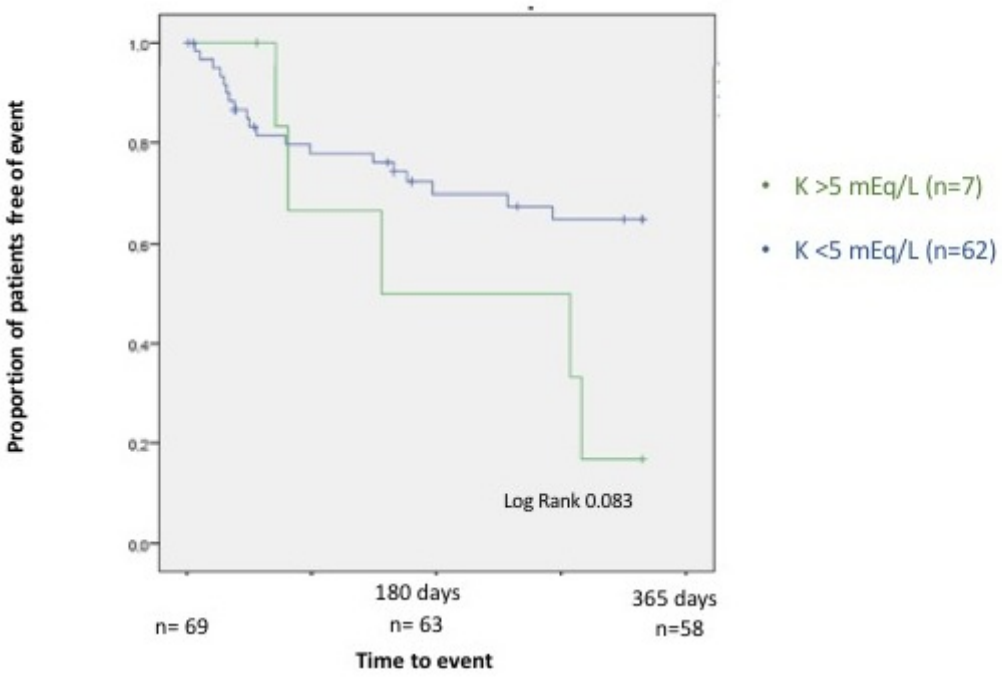

Patients hospitalized at Fundación Jiménez Díaz in Madrid, between July 17th, 2017 and November 11th, 2018, with a diagnosis of heart failure
n= 209
Set of criteria:
*Inclusion
**Exclusion
Patient rejection (n=41)
n= 97 Excluded due to: severe COPD (20), Systemic conditions (17), Severe airway infection (16), dementia (13), anemia (8), advanced stage cancer (7), concomitant cancer and anemia (6), DPLD (4), PTE (1), Surgery upcoming (1) or other infections (3)
Not able to confirm nor deny MG n=2
Patients enrolled n=71
Patients analyzed n=69



- Betablockers (n= 30)
- No Betablockers (n=39)



- ACEI/ARB (n=34)
- No ACEI/ARB (n=35)


Proportion of patients free of event
1.0
0.8
0.6
0.4
0.2
0.0
Log Rank 0.083
180 days
365 days
n= 69
n= 63
n=58
Time to event
K >5 mEq/L (n=7)
K <5 mEq/L (n=62)