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# Outcomes of patients with heart failure with preserved ejection fraction discharged on treatment with neurohormonal antagonists after an episode of decompensation

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## ARTICLE INFO

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## ABSTRACT

*Aims:* To analyze the frequency with which patients with heart failure with preserved ejection fraction (HFpEF) discharged after an acute heart failure (AHF) episode are treated with antineurohormonal drugs (ANHD), the variables related to ANHD prescription and their relationship with outcomes.

*Methods:* We included consecutive HFpEF patients (left ventricular ejection fraction ≥50%) discharged after an AHF episode from 45 Spanish hospitals whose chronic medications and treatment at discharge were available. Patients were classified according to whether they were discharged with or without ANHD, including beta-blockers (BB), renin-angiotensin-aldosterone-system inhibitors (RAASi) and mineralcorticosteroid-receptor antagonists (MRA). Co-primary outcomes consisted of 1-year all-cause mortality and 90-day combined adverse event (revisit to emergency department –ED-, hospitalization due to AHF or all-cause death). Secondary outcomes were 90-day adverse events taken individually. Adjusted associations of ANHD treatment with outcomes were calculated.

*Results:* We analyzed 3,305 patients with HFpEF (median age: 83, 60% women), 2,312 (70%) discharged with ANHD. The ANHD most frequently prescribed was BB (45.8%). The 1-year mortality was 26.9% (adjusted HR for ANHD patients:1.17, 95%CI=0.98-1.38) and the 90-day combined adverse event was 54.4% (HR=1.14, 95%

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[1] Consult Appendix 1 to see the complete list of the ICA-SEMES Research Group (Research group on Acute Heart Failure of the Spanish Society of Emergency Medicine) members

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CI=0.99-1.31). ED revisit was significantly increased by ANHD (HR=1.15, 95%CI=1.01-1.32). MRA and BB were associated with worse results in some co-primary or secondary endpoints, while RAASi (alone) reduced 90-day hospitalization (HR=0.73, 98%CI=0.56-0.96).
*Conclusion:* 70% of HFpEF patients are discharged with ANHD after an AHF episode. ANHD do not seem to reduce mortality or adverse events in HFpEF patients, only RAASi could provide some benefits, reducing the risk of hospitalization for AHF.

## 1. Introduction

Heart failure (HF) is an important health problem with elevated socio-health care costs. This disease is highly prevalent in the people over the age of 65 years and constitutes the first cause of hospitalization in this population. In addition, mortality and rehospitalization associated with decompensations such as acute heart failure (AHF) are high, even in patients with low risk HF (1-3). During the last decades, there has been an increase in the percentage of patients with HF with preserved ejection fraction (HFpEF), that it is currently defined by a left ventricular ejection fraction (LVEF) greater than or equal to 50% (4). The physiopathology of HFpEF is complex and heterogeneous and is related to different factors which act independently and converge into a systemic inflammatory state, with the increase in its prevalence being related to the aging of the population (5,6). At present, in many countries more than 50% of the cases of HF correspond to the HFpEF type.

Although the clinical presentation and diagnosis of HFpEF are similar to what occurs in HF with reduced ejection fraction (HRrEF, defined by LVEF <40%), it is considered a different entity at both a physiopathological and prognostic level, and there are significant differences in the treatment of both types of HF (4,7). Thus, neurohormonal antagonists such as beta-blockers (BB), renin angiotensin aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists (MRA) are used in the treatment of HFrEF and have shown to improve disease outcomes. These neurohormonal antagonists are generically called disease-modifying drugs as they are able to improve outcomes in patients with HFrEF, and the guidelines of clinical practice recommend their use (class of recommendation I, level of evidence A) (4,8). On the other hand, studies and clinical trials evaluating the effects of antineurohormonal drugs on HFpEF have shown null impact on outcomes. Nonetheless, in the usual clinical practice it is common to find patients with HFpEF receiving ANHD in order to treat other intercurrent diseases in which these drugs are indicated or for other less clear reasons (9). Despite this, very few studies have evaluated their impact on outcomes in the scenario of usual clinical practice. Therefore, the aim of this study was to analyze the frequency with which HFpEF patients discharged after an AHF episode receive treatment with ANHD. We also analyzed the variables related to this prescription and their relationship with the principal prognostic indicators, including readmission to the ED due to AHF, need for hospitalization and death following the index event.

## 2. Methods

### 2.1. Setting

The present study is a subanalysis of the EAHFE Registry. The EAHFE Registry was initiated in 2007 and every 2-3 years it carries out a 1-2-month recruitment period of all consecutive patients diagnosed with AHF in Spanish EDs participating in the project. To date, 6 recruitment phases (in 2007, 2009, 2011, 2014, 2016 and 2018) have been performed with the participation of 45 EDs from community and university hospitals across Spain (representing about 15% of the Spanish public health care system hospitals), enrolling a total of 18,370 AHF patients. Details of patient inclusion have been extensively reported elsewhere [3, 10, 11]. The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions. The only exclusion criteria for inclusion is the development of AHF during ST-elevation myocardial infarction (STEMI), as many of these patients go straight to the cath lab for revascularization, bypassing the ED.

### 2.2. Study design and variables recorded

The present analysis included all patients discharged alive after an episode of AHF with a LVEF of 50% or more recorded in an echocardiography performed during the 6 months prior to decompensation or that had been recorded during the current admission. To be included in the present analysis, in addition to the clinical criteria required to be included in the EAHFE registry, determination of natriuretic peptides during ED stay or hospitalization was necessary, and blood concentrations > 100 ng/L (for BNP) or 450 ng/L (for NT-proBNP) were required for final inclusion (4). Of the 6 phases of the EAHFE Registry, only patients included in phases 4, 5 and 6 were considered for this study, as data regarding chronic treatments before decompensation and treatments provided after discharge for the current episode were only included in the datasheet from phase 4 onwards. Two groups were formed according to whether patients were discharged with or without ANHD. We considered antineurohormonal drugs: RAAS inhibitors, BB and MRA, either alone or in any combination, and at any dosage.

Forty-eight independent variables were collected including demographic data, baseline status, acute episode characteristics and management provided in the ED. All the variables were prospectively recorded in a specific datasheet during ED stay, and the definitions are included in supplemental Table 1. To assess the severity of the current episode of decompensation we used the MEESSI score, a clinical score that has demonstrated very good prediction of 30-day mortality in patients with AHF using clinical data recorded in the ED (3,10). The MEESSI score is calculated from 13 variables recorded during the first patient assessment in the ED (in order of importance: Barthel index, systolic blood pressure, age, NT-proBNP, potassium, troponin, NYHA class, respiratory rate, low output symptoms, oxygen saturation, concurrent acute coronary syndrome, left ventricular hypertrophy in the electrocardiogram [ECG] and creatinine).

### 2.3. Outcomes

We defined two co-primary endpoints: the 1-year all-cause mortality and the 90-day post-discharge combined adverse event, which was constituted by all-cause death, hospitalization due to AHF or ED revisit due to AHF, whichever happened first. Additionally, each of these three 90-day adverse events was individually considered as a secondary outcome. The revisit and hospitalization event adjudication was based on the clinical judgment of the attending physicians stated in the ED report of the revisit or in the discharge report after hospitalization, which were reviewed by the researchers at a local level. The starting point was the day of patient discharge after the AHF index event, irrespective of whether discharge was made directly from the ED or after hospitalization. The vital status of the patients and hospitalization and ED revisits were ascertained by consultation of medical records, which are electronically accessible in nearly all Spanish communities. Moreover, we contacted patients or relatives through phone call when no clear data was present in the clinical history or access was not possible. Death was also verified through the Spanish public health insurance database that covers >99% of the Spanish population, as every patient

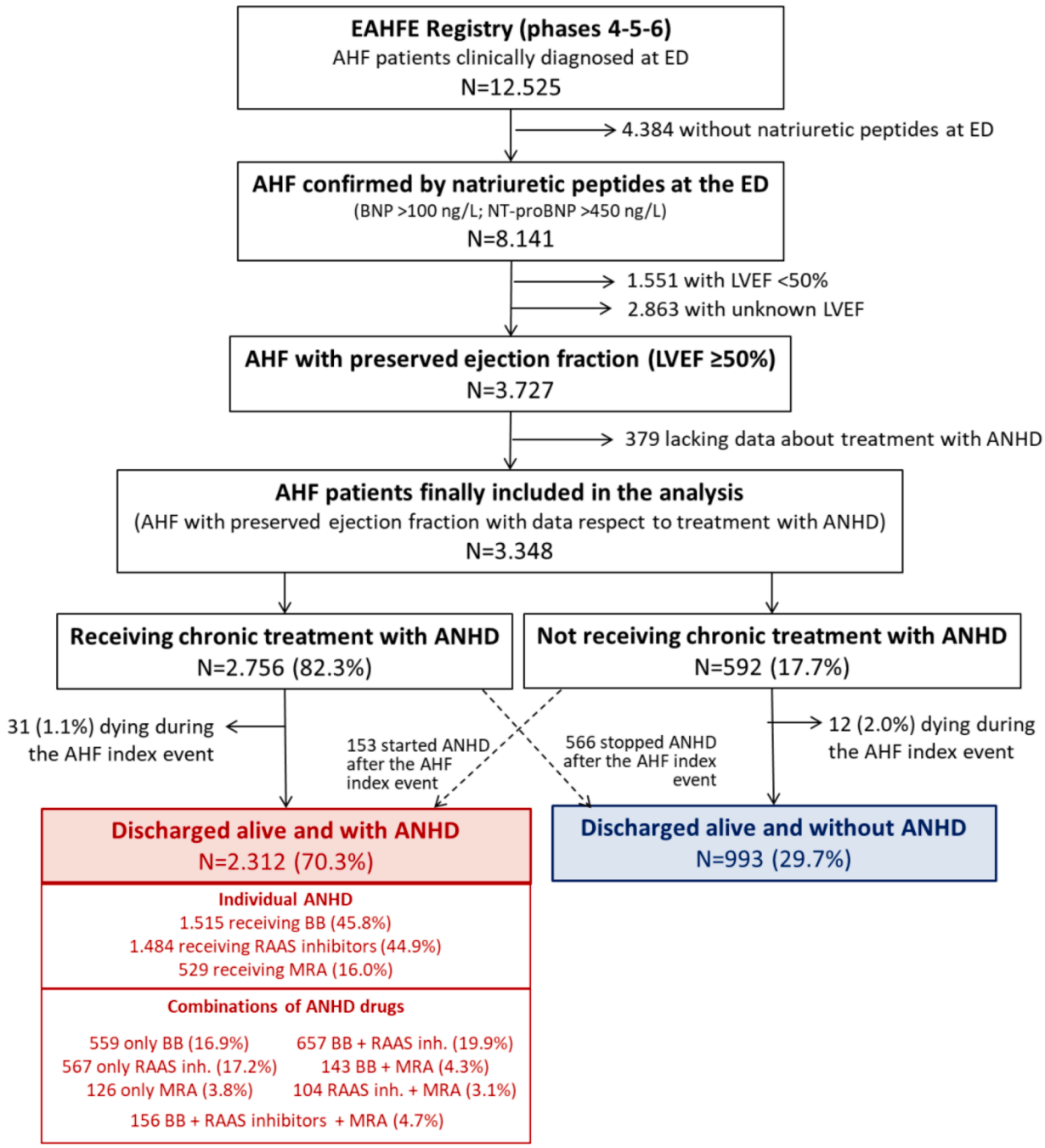



**Fig. 1.** Flow chart for patient inclusion.
ANHD: antineurohormonal drugs; ED: emergency department; AHF: acute heart failure; LVEF: left ventricle ejection fraction; BB: beta-blockers; RAAS: renin-angiotensin-aldosterone system; inh.: inhibitors; MRA: mineralcorticosteroid-receptor antagonists.

death is immediately retired from this database at the exact time point that death occurs. Every event adjudication was performed at a local level by the principal investigator of each hospital.

### 2.4. Statistical analysis

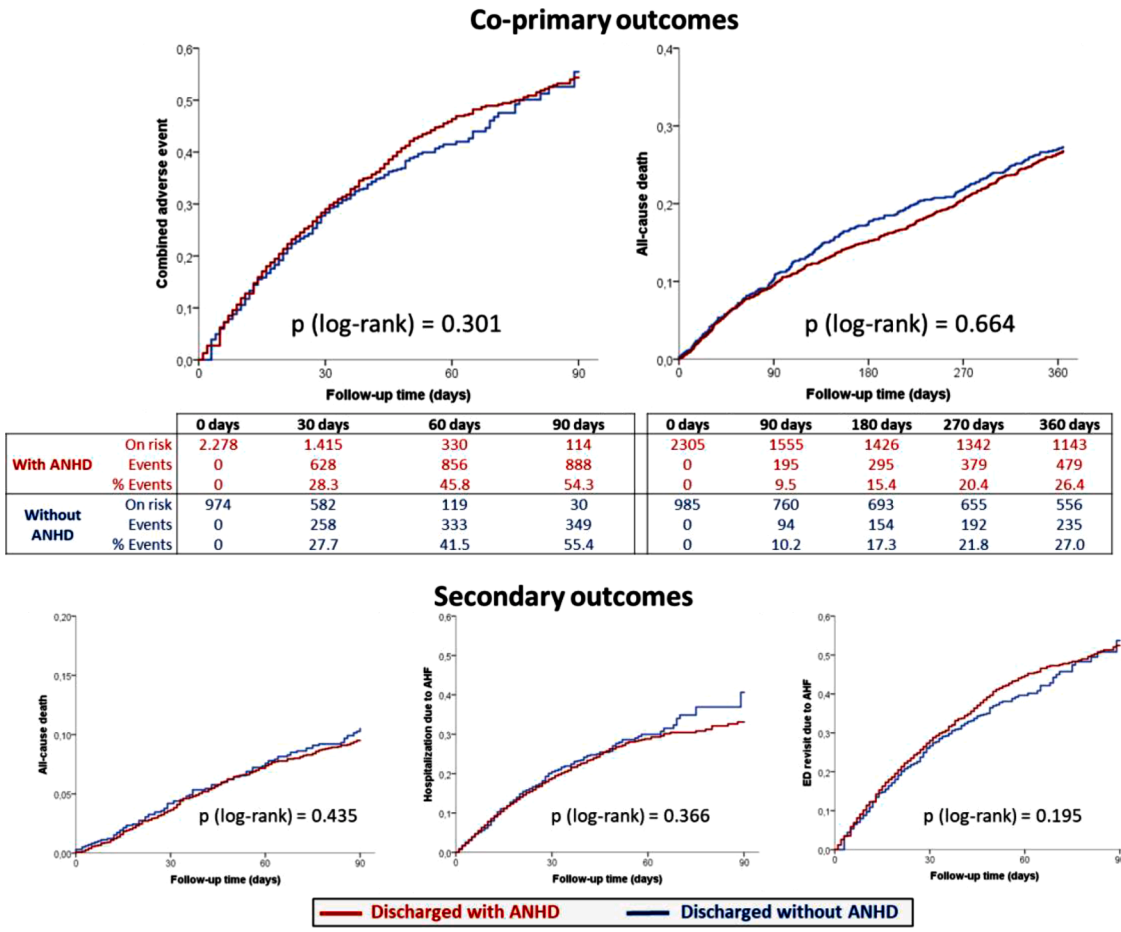
Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed, and categorical variables as absolute values and percentages. Comparison between groups was carried out using one-way ANOVA for continuous variables (or by Mann-Whitney non-parametrical test if not normally distributed) and the chi square test (or Fisher exact test, if needed) for categorical variables. Co-primary and secondary outcomes were explored using survival tables and Kaplan-Meier curves, and comparison between curves was made using the log-rank test.

Unadjusted and adjusted associations of treatment with ANHD with outcomes were calculated using Cox regression models and expressed as hazard ratios (HR) with 95% confidence interval (CI). Adjustment was performed for age and sex and for any variable regarding baseline status, clinical characteristic of decompensation and management in the ED that were found to be statistically different between patients with and without ANHD in the univariable analysis. Missing values in the variables included in the adjusted models were replaced using the multiple imputation technique, generating 10 datasets in which there were no missing values among all the variables included in the adjustment. In the adjusted model for 1-year mortality, we analyzed the HR for each

**Table 1**
Characteristics of patients with heart failure with preserved ejection fraction (HFpEF) included in the study and comparison according to whether they were discharged with or without antineurohormonal drugs.

| | Total N=3,305 n (%) | Missing data n (%) | With ANHD N=2,312 n (%) | Without ANHD N=993 n (%) | p |
|---|---|---|---|---|---|
| **Demographic data** | | | | | |
| Age (years) (median (IQR) | 83.4 (77.5-87.7) | 0 | 83 (77-87.3) | 84.5 (78.8-88.5) | **0.00** |
| Female sex | 1993 (60.5) | 15 (0.5) | 1404 (60.9) | 589 (59.6) | 0.50 |
| **Basal status of the patient** | | | | | |
| **Comorbidities** | | | | | |
| Arterial hypertension | 2823 (87.4) | 5 (0.2) | 2021 (87.4) | 802 (80.8) | **0.00** |
| Diabetes mellitus | 1350 (40.8) | 5 (0.2) | 973 (42.1) | 377 (38) | **0.03** |
| Dyslipidemia | 1607 (48.6) | 5 (0.2) | 1150 (49.7) | 457 (46) | 0.05 |
| Ischemic cardiomyopathy | 839 (25.4) | 5 (0.2) | 622 (26.9) | 217 (21.9) | **0.00** |
| Chronic renal disease | 932 (28.2) | 5 (0.2) | 650 (28.1) | 282 (28.4) | 0.87 |
| Cerebrovascular disease | 407 (12.3) | 6 (0.2) | 301 (13) | 106 (10.7) | 0.06 |
| Atrial fibrillation | 2069 (62.6) | 5 (0.2) | 1453 (62.8) | 616 (62) | 0.66 |
| Valve disease | 1095 (33.1) | 5 (0.2) | 774 (33.5) | 321 (32.3) | 0.52 |
| Peripheral artery disease | 329 (10) | 5 (0.2) | 239 (10.3) | 90 (9.1) | 0.26 |
| Chronic obstructive pulmonary disease | 806 (24.4) | 6 (0.2) | 523 (22.6) | 283 (28.5) | **0.00** |
| Dementia | 302 (9.1) | 6 (0.2) | 213 (9.2) | 89 (9) | 0.82 |
| Neoplasia | 477 (14.4) | 5 (0.2) | 320 (13.8) | 157 (15.8) | 0.14 |
| Hepatic cirrhosis | 48 (1.5) | 8 (0.2) | 39 (1.7) | 9 (0.9) | 0.09 |
| Previous heart failure | 2352 (75) | 174 (5.3) | 1627 (74.5) | 725 (76.2) | 0.32 |
| **Functional capacity** | | | | | |
| Barthel index (points) (median (IQR)) | 90 (70-100) | 110 (3.3) | 90 (75-100) | 90 (70-100) | **0.01** |
| NYHA Class III-IV | 788 (24.4) | 78 (2.4) | 541 (23.9) | 247 (25.6) | 0.29 |
| LVEF (%) (median (IQR)) | 60 (55-65) | 211 (6.4) | 60 (55-65) | 57 (55-65) | **0.01** |
| **Chronic treatment** | | | | | |
| Diuretics | 2297 (69.5) | 5 (0.2) | 1579 (68.3) | 718 (72.3) | **0.02** |
| ACEIs or ARA-II | 1823 (55.2) | 5 (0.2) | 1461 (63.2) | 362 (36.5) | **0.00** |
| Betablockers | 1720 (52.1) | 6 (0.2) | 1377 (59.6) | 343 (34.5) | **0.00** |
| Aldosterone receptor antagonists | 500 (15.1) | 5 (0.2) | 387 (16.7) | 113 (11.4) | **0.00** |
| Digoxin | 455 (13.8) | 5 (0.2) | 301 (13) | 154 (15.5) | 0.06 |
| **Characteristics of the decompensation episode** | | | | | |
| **Precipitating factor** | | | | | |
| Infection | 1359 (41.8) | 60 (1.8) | 894 (39.4) | 465 (47.5) | **0.00** |
| Rapid atrial fibrillation | 480 (14.8) | 62 (1.9) | 361 (15.9) | 119 (12.2) | **0.01** |
| Anemia | 238 (7.3) | 60 (1.8) | 176 (7.7) | 62 (6.3) | 0.16 |
| Hypertensive crisis | 165 (5.1) | 60 (1.8) | 135 (5.9) | 30 (3.1) | **0.00** |
| Non-adherence to pharmacological or dietetic treatment | 76 (2.3) | 60 (1.8) | 62 (2.7) | 14 (1.4) | **0.02** |
| | 53 (1.6) | 36 (1.1) | 43 (1.9) | 10 (1) | 0.07 |
| Acute coronary syndrome (either angina or non-STEMI) | | | | | |
| **Vital signs at ED arrival** | | | | | |
| SBP (mmHg) (median (IQR)) | 139 (123-156) | 28 (0.8) | 140 (124-158) | 138 (122-154) | **0.01** |
| Heart rate (bpm) (median (IQR)) | 83 (70-100) | 70 (2.1) | 82 (70-100) | 83 (70-100) | 0.39 |
| Oxygen saturation (%) (median (IQR)) | 94 (90-97) | 84 (2.5) | 94 (90-97) | 94 (90-96) | **0.02** |
| **Analyses** | | | | | |
| Hemoglobin (g/L) (median (IQR)) | 11.9 (10.6-13.3) | 10 (0.3) | 12 (10.6-13.3) | 11.8 (10.6-13.2) | 0.09 |
| Creatinine (mg/dL) (median (IQR)) | 1.12 (0.86-1.5) | 20 (0.6) | 1.1 (0.85-1.5) | 1.18 (0.89-1.58) | **0.00** |
| Hyponatremia (<135 mmol/L) | 436 (13.6) | 93 (2.8) | 316 (14.1) | 120 (12.4) | 0.21 |
| Hyperpotassemia (>5 mmol/L) | 410 (13.3) | 216 (6.5) | 291 (13.4) | 119 (13) | 0.77 |
| Raise troponin (>99$^{th}$ percentile) | 997 (50.2) | 1324 (40) | 696 (48.7) | 301 (53.9) | **0.04** |
| NT-proBNP (pg/mL) (median (IQR)) | 3298 (1800-6693) | 176 (5.3) | 3279 (1800-6514) | 3347 (1809-7129) | 0.21 |
| **Global severity of decompensation episode*** | | 1345 (40.6) | | | 0.78 |
| - Low risk | 837 (42.6) | | 611 (42.8) | 226 (42) | |
| - Intermediate risk | 831 (42.3) | | 604 (42.3) | 227 (42.2) | |
| - High risk alto | 200 (10.2) | | 146 (10.2) | 54 (10) | |
| - Very high risk | 97 (4.9) | | 66 (4.6) | 31 (5.8) | |
| **Management in the ED** | | | | | |
| **Treatment in the ED** | | | | | |
| Endovenous diuretic | 2710 (83.8) | 75 (2.3) | 1924 (85.2) | 786 (80.4) | **0.00** |
| Endovenous nitroglycerine | 256 (7.9) | 76 (2.3) | 191 (8.5) | 65 (6.7) | 0.08 |
| Morphine | 155 (4.8) | 75 (2.3) | 99 (4.4) | 56 (5.7) | 0.10 |
| Digoxin | 363 (11.2) | 75 (2.3) | 274 (12.1) | 89 (9.1) | **0.01** |
| Amiodarone | 76 (2.3) | 75 (2.3) | 50 (2.2) | 26 (2.7) | 0.45 |
| Inotrops/ vasopressors | 13 (0.4) | 76 (2.3) | 10 (0.4) | 3 (0.3) | 0.57 |
| Non-invasive ventilation | 217 (6.7) | 75 (2.3) | 147 (6.5) | 70 (7.2) | 0.50 |
| **Patient destination** | | | | | |
| Hospitalization | 2642 (79.9) | 5 (0.2) | 1834 (79.3) | 808 (81.4) | 0.18 |
| Length of hospital stay (days) (median (IQR)) | 6 (2-10) | 17 (0.5) | 6 (2-10) | 6 (3-11) | **0.01** |

ANHD antineurohormonal drugs; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; ACEI: angiotensin- converting enzyme Inhibitors; ARAII: Angiotensin receptor antagonists-II. STEMI: ST-elevation myocardial infarction. SBP: systolic blood pressure; ED: emergency department; IQR: interquartile range.
The p values in bold highlight the differences considered statistically significant.
* The severity of the episode was estimated with the MEESSI scale which classifies the risk of death of a patient with left cardiac insufficiency in the 30 days following presentation to the emergency department based on 13 variables obtained at arrival to the emergency department: age, Barthel index, NYHA respiratory class, systolic blood pressure, respiratory frequency, oxygen saturation, signs of low cardiac output, episode triggered by an acute coronary syndrome, left ventricular hypertrophy in the ECG and NT-proBNP, troponin, creatinine and potassium values.




| | | 0 days | 30 days | 60 days | 90 days | 0 days | 90 days | 180 days | 270 days | 360 days |
|---|---|---|---|---|---|---|---|---|---|---|
| With ANHD | On risk | 2.278 | 1.415 | 330 | 114 | 2305 | 1555 | 1426 | 1342 | 1143 |
| | Events | 0 | 628 | 856 | 888 | 0 | 195 | 295 | 379 | 479 |
| | % Events | 0 | 28.3 | 45.8 | 54.3 | 0 | 9.5 | 15.4 | 20.4 | 26.4 |
| Without ANHD | On risk | 974 | 582 | 119 | 30 | 985 | 760 | 693 | 655 | 556 |
| | Events | 0 | 258 | 333 | 349 | 0 | 94 | 154 | 192 | 235 |
| | % Events | 0 | 27.7 | 41.5 | 55.4 | 0 | 10.2 | 17.3 | 21.8 | 27.0 |

**Fig. 2.** Kaplan-Meier analysis of the co-primary and secondary outcomes in patients with heart failure with preserved ejection fraction (HFpEF) according to whether they were discharged with or without antineurohormonal drugs.
ED: emergency department; ANHD: antineurohormonal drugs; AHF: acute heart failure.

individual year quarter by replacing all patients surviving at the end of the 90-day quarter period at the starting point (day 0) of the next quarter and then calculating the HR for the 90-day mortality of the next year quarter. In addition, we also compared outcomes in a propensity score (PS) matched cohort of paired patients. The PS was calculated by logistic regression (including age, sex, and the independent variables that significantly differed between groups, defined as a $p < 0.05$) and determined the probability that participants would receive ANHD based on these individual characteristics. Patients were then paired (1:1) based on the nearest neighbor matching with a caliper of 0.1.

We carried out multiple subgroup analyses in the adjusted models comparing patients receiving any combination of ANHD (BB, RAAS inhibitors and MRA) with patients without ANHD in order to uncover individual medications (or specific combinations) achieving statistical differences in any co-primary or secondary outcomes. For the primary outcomes, we also explored the presence of interaction for four variables (age, sex, ischemic cardiomyopathy as comorbidity, and de novo versus worsening HF), in order to uncover whether ANHD could exert a differential effect on a particular subgroup of patients. We also performed some sensitivity analyses in the adjusted models by including only those patients that initiate treatment with ANHD after AHF decompensation (i.e., excluding patients receiving chronic ANHD before decompensation) and compared them with those that were maintained without any ANHD after discharge from the AHF episode.

Statistical significance was accepted if the p value was less than 0.05 or if the 95%CI of the HR excluded the value 1. Since this was an exploratory study, a pre-hoc sample size calculation was not made. All calculations were made using SPSS v24.0 software (IBM, Armonk, NY, USA).

### 2.5. Ethics

The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, 160/15 and 205/17. Due to the non-interventional design of the registry, Spanish legislation allows central Ethical Committee approval, accompanied by notification to the local Ethical Committees. All participating patients gave informed consent to be included in the registry and to be contacted for follow-up. The present study was carried out in strict compliance with the principles of the Declaration of Helsinki.

## 3. Results

Of the 12,525 patients diagnosed with AHF in the participating EDs during phases 4, 5 and 6 of the EAHFE Registry, 3,305 patients with HFpEF fulfilled the inclusion criteria and were finally included. The mean age was 83 years (IQR 77-88), and 60% were women. Of these, 2,312 patients were receiving ANHD (70.3%), and the 993 remaining patients made up the group without ANHD (29.7%). The ANHD most frequently prescribed was BB (45.8%), and the most frequent combination was BB plus RAAS inhibitors (19.9%) (Fig. 1).

The univariable analysis between patients with and without ANHD showed significant differences in 23 of the 49 variables analyzed (Table 1). The group receiving ANHD was younger, had a higher presence of hypertension, diabetes mellitus and ischemic cardiomyopathy,

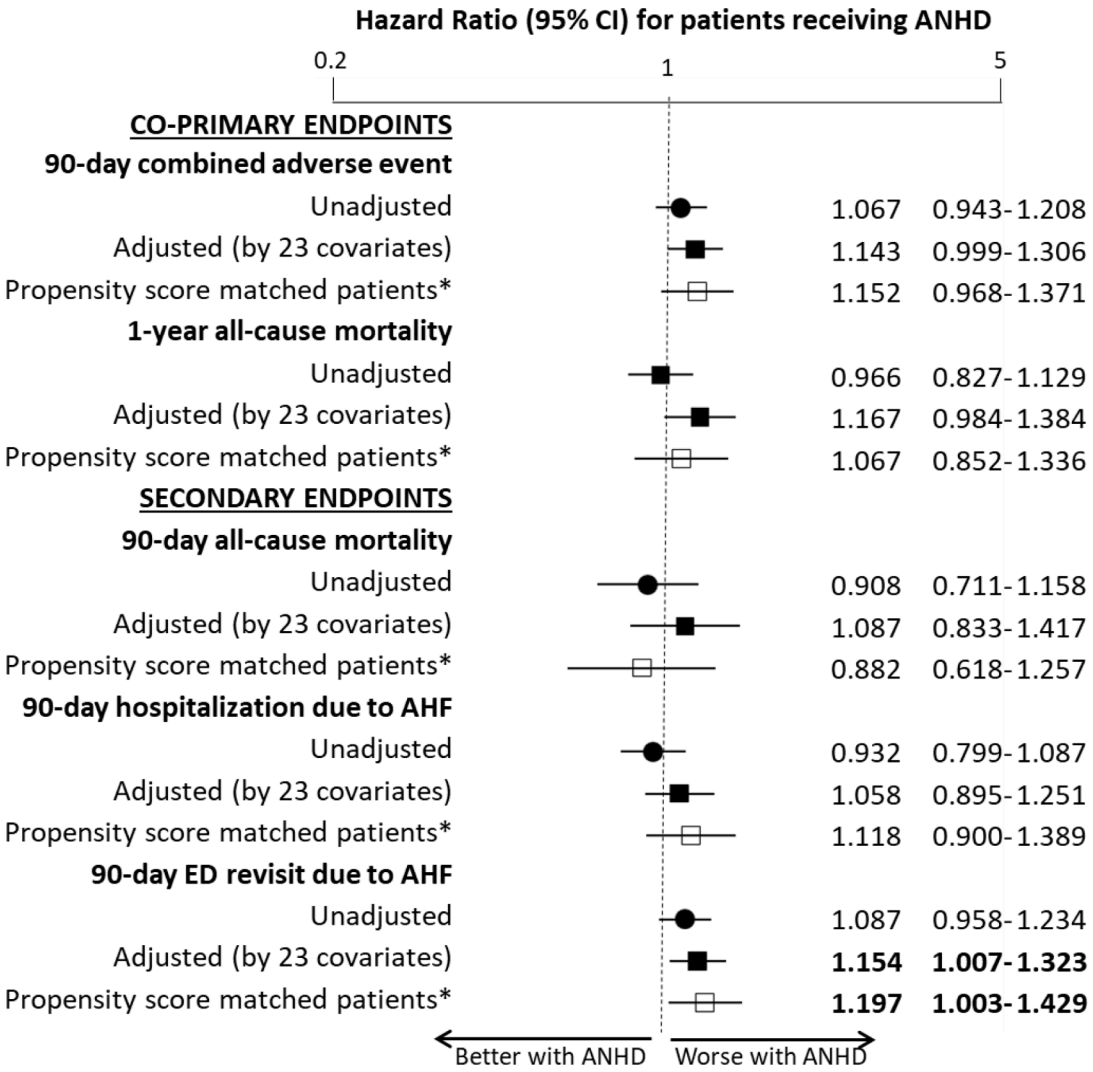



**Fig. 3.** Unadjusted and adjusted hazard ratios for patients with heart failure with preserved ejection fraction (HFpEF) receiving antineurohormonal drugs for the co-primary and secondary outcomes.
*Propensity score matching provided 711 pairs of patients matched by demographic, basal status, characteristics of the decompensation and management in the emergency department. ANHD: antineurohormonal drugs; AHF: acute heart failure; ED: emergency department. P values in bold highlight differences considered statistically significant.

less functional capacity, and decompensation was more frequent due to tachyarrhythmia, hypertensive crisis or incompliance with pharmacological or dietetic treatments. There were no significant differences between the two groups with respect to the severity of the AHF episode estimated using the MEESSI scale or by the need for hospitalization. In the case of hospitalization, the median hospital stay was longer in the group without ANHD.

The risk of death at 1 year was 26.9%, and the risk of experiencing a combined adverse event at 90 days was 54.4%, while the risk of 90-day death, hospitalization and ED-revisit individually considered was 9.8%, 35.1% and 52.6%, respectively. Survival curves for patients with and without ANHD were not statistically different for any of these co-primary or secondary outcomes (Fig. 2). After adjustment, there was also no statistically significant association between treatment with ANHD and 1-year mortality (HR=1.167 for patients with ANHD, 95% CI=0.984-1.384) or the 90-day combined adverse event (HR=1.143, 95%CI=0.999-1.306). With respect to secondary outcomes, only ED revisit was statistically greater in the adjusted model in patients with ANHD (HR=1.154, 95%CI=1.007-1.323), while there were no differences in the risk of death or rehospitalization (Fig. 3). The analysis of outcomes in the PS matched cohort, which provided 711 pairs of patients with balanced possibilities of receiving ANHD, rendered very similar results (Fig. 3).

When the ANHD were analyzed individually in relation to their association with outcomes (Table 2), we observed that MRA alone and BB, alone or combined with other ANHD, were associated with worse results in some co-primary and secondary endpoints. When assessing the association of ANHD with 1-year mortality for every individual year quarter, we observed that a negative impact becomes more evident after the second quarter for ANHD considered altogether as well as for the BB and MRA considered individually (Fig. 4). On the other hand, the only ANHD positive impact for HFpEF patients was observed in those who exclusively received RAAS inhibitors, showing a significant reduction in the risk of hospitalization for a new AHF episode at 90 days (HR=0.735, 98%CI=0.564-0.957). We did not find interaction for the co-primary outcomes for any subgroup of patients based on age, sex, ischemic cardiomyopathy as a comorbidity or de novo versus worsening HF (Fig. 5).

## 4. Discussion

This study has three main findings. The first was that there were no significant changes in 1-year mortality or 90-day combined adverse

**Table 2**
Adjusted hazard ratios for patients with heart failure with preserved ejection fraction (HFpEF) receiving antineurohormonal drugs for the co-primary and secondary outcomes considered in the present study.

| | Co-primary endpoints | | Secondary endpoints | | |
|---|---|---|---|---|---|
| | 90-day combined adverse event | 1-year all-cause death | 90-day all-cause death | 90-day hospitalization due to AHF | 90-day ED revisit due to AHF |
| | HR (95% CI)* | HR (95% CI)* | HR (95% CI)* | HR (95% CI)* | HR (95% CI)* |
| Receiving any antineurohormonal drug | 1.136 (0.993-1.298) | 1.181 (0.997-1.400) | 1.087 (0.833-1.417) | 1.058 (0.895-1.251) | **1.154 (1.007-1.323)** |
| Receiving BB (either alone or in combination) | **1.407 (1.157-1.711)** | 1.247 (0.963-1.616) | 1.119 (0.755-1.658) | **1.489 (1.168-1.898)** | **1.398 (1.145-1.707)** |
| Receiving RAAS inhibitor (either alone or in combination) | 0.989 (0.807-1.211) | 1.004 (0.767-1.314) | 0.989 (0.629-1.553) | 0.817 (0.627-1.065) | 1.018 (0.828-1.251) |
| Receiving MRA (either alone or in combination) | 1.089 (0.804-1.475) | 1.398 (0.971-2.105) | 1.057 (0.578-1.934) | 1.067 (0.731-1.557) | 1.130 (0.830-1.540) |
| Receiving only BB | **1.421 (1.172-1.723)** | 1.222 (0.948-1.575) | 1.174 (0.800-1.725) | **1.503 (1.182-1.911)** | **1.415 (1.162-1.722)** |
| Receiving only RAAS inhibitor | 0.945 (0.773-1.154) | 1.059 (0.815-1.376) | 0.958 (0.620-1.480) | **0.735 (0.564-0.957)** | 0.974 (0.794-1.194) |
| Receiving only MRA | 1.074 (0.780-1.477) | **1.579 (1.096-2.274)** | 1.280 (0.703-2.329) | 0.980 (0.655-1.466) | 1.069 (0.769-1.484) |
| Receiving the combination of BB + RAAS inhibitor | **1.236 (1.013-1.507)** | 1.148 (0.872-1.510) | 1.224 (0.798-1.878) | 1.187 (0.920-1.532) | **1.226 (1.001-1.502)** |
| Receiving the combination of BB + MRA | 1.008 (0.724-1.403) | 1.271 (0.836-1.933) | 0.895 (0.457-1.752) | 1.056 (0.696-1.601) | 1.074 (0.769-1.499) |
| Receiving the combination of RAAS inhibitor + MRA | 0.966 (0.675-1.381) | 0.795 (0.468-1.379) | 0.506 (0.179-1.432) | 0.903 (0.575-1.420) | 1.067 (0.747-1.524) |
| Receiving the combination of BB + RAAS inhibitor + MRA | 0.949 (0.689-1.307) | 1.304 (0.870-1.953) | 1.309 (0.696-2.460) | 0.758 (0.484-1.189) | 0.975 (0.703-1.353) |

AHF: acute heart failure; ANHD: antineurohormonal drugs; BB: beta-blocker; RAAS: renin-angiotensin system inhibitors; MRA: mineralcorticosteroid-receptor antagonist

* Hazard ratios were performed for age and sex, hypertension, diabetes mellitus, ischemic cardiomyopathy and chronic obstructive pulmonary disease as comorbidities, Barthel index at baseline, left ventricular ejection fraction, chronic treatment with loop-diuretic, renin-angiotensin system inhibitors and beta-blockers and mineralcorticosteroid-receptor antagonists, infection, rapid atrial fibrillation, hypertensive crisis and dietetic/pharmacologic transgression as precipitants of the index episode of acute heart failure, systolic blood pressure, pulsioxymetry, creatinine and raised troponin at emergency department arrival, and treatment with intravenous diuretics and digoxin in the emergency department, and length of hospitalization.

events among patients with HFpEF treated with ANHD, although a significant 15% increase in ED revisit due to AHF was noted. Second, treatment with BB (alone or in combination) was associated with significant increases of between 25% and 50% in mortality, combined adverse events, hospitalizations and ED revisits for AHF. Additionally, when MRA were used alone, a 58% of increase in 1-year mortality was observed. And third, treatment with RAAS inhibitors showed a neutral effect in relation to most of the endpoint variables, and even when these drugs were received alone (in the absence of BB or MRA cotreatment), this was related to a significant reduction of 27% in hospitalization due to AHF.

In the ANHD group (formed by patients receiving BB, RAAS inhibitor or MRA, alone or in combination), the elevated percentage of hypertension (87%) and cases in which decompensation of hypertension became a precipitating factor for the hypertension episode were of note. This suggests that hypertension in these patients was not adequately controlled. In addition, this could justify why almost 20% of patients with HFpEF that were not on chronic medication with ANHD initiated treatment with ANHD at discharge with the aim of achieving better control of hypertension, since BB and RAAS inhibitors make up an essential part of the treatment of hypertension. Likewise, it was of note that although the greater risk of ED revisit due to a new AHF episode among the patients with HFpEF with ANHD could have been related to the greater percentage of comorbidities, this group was actually younger, had better LVEF and renal function and lower troponin levels. In addition, these patients presented less physical fragility (since they had a better Barthel index), and fragility is related to worse prognosis (13). Moreover, this increase in risk of ED revisit in the ANHD group was observed in the adjusted model in which these differences were taken into account. Therefore, we have no clear explanation for this finding and were unable to find any bibliographic references with respect to the effect of treatment with ANHD (considered globally) in patients with HFpEF on the results in the setting of real clinical practice.

In addition, the contribution of each ANHD to outcomes is difficult to determine. However, of note was the increase of almost 30% in ED revisits, hospitalizations and combined adverse events in association with the use of BB, that could be of up to 50% when BB are used alone, with no other ANHD in combination. Treatment with BB in HFpEF is especially controversial because of the limited number of studies available and the contradictory results (14-21), and also because most studies and reviews also include patients with LVEF between 40-49% (currently classified as HF with mid-range ejection fraction, HFmrEF). In these latter studies, treatment with ANHD tends to improve the clinical manifestations (mainly dyspnea), echocardiographic results and mortality, especially when the patient profile is similar to that of patients with HFrEF in whom treatment with BB is mandatory (20). Thus, in the study by Zheng *et al.*, which included patients with a LVEF greater than 40%, the use of BB significantly reduced the mortality by 22% compared to placebo (17). In the meta-analysis by Liu *et al.*, which also included patients with an LVEF greater than 40%, there was a significant reduction in all-cause mortality of 9%, but hospitalization did not decrease (18). Very recently, Kimmoun *et al.* analyzed outcomes of more than 15 million of AHF episodes from 285 studies and found positive correlations between treatment with BB (alone or, ideally, combined with RAAS inhibitors) and AHF survival (but not rehospitalization), and this relationship was similarly obtained in patients with LVEF $\geq$40% and with LVEF <40% (21). Conversely, studies in patients with a LVEF greater than 50% did not find benefits with the use of BB, and some studies even reported increases in hospitalization of greater than 70% (15,16), in line with our findings. The use of BB is not advised by other authors due to the risk of adverse cardiovascular events in relation to an increase in central venous pressure and prolonged diastolic filling. These events increase ventricle load, plasma natriuretic peptide concentrations and bradyarrhythmias due to impairment of the conduction system related to older age (19).

In contrast to BB, patients with HFpEF treated only with RAAS

**Supplemental Table 1**
Glossary of the variables included in the present study.

| | |
|---|---|
| **DEMOGRAPHICS** | |
| **Age** | Age calculated as the difference in decimal years between the date of inclusion in the study and the date of birth. |
| **Sex** | Male/Female |
| **MEDICAL HISTORY** | |
| **Hypertension** | Indicate if the patient has arterial hypertension because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Diabetes Mellitus** | Indicate if the patient has diabetes mellitus because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Dyslipemia** | Indicate if the patient has been diagnosed with dyslipemia because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Ischemic cardiomyopathy** | Indicate if the patient has any form of ischaemic heart disease (acute coronary syndrome without an elevation of the ST segment, acute coronary syndrome with an elevation of the ST segment unstable angina, stable angina, etc.) because this is shown under previous clinical history or the patient is receiving specific treatment. |
| **Chronic kidney disease** | Indicate if the patient has chronic renal insufficiency or chronic kidney disease or if analyses over the previous year show creatinine values >2 mg/dL. |
| **Cerebrovascular disease** | Indicate if the patient has had a previous cerebrovascular accident or cerebrovascular disease because this is described in the clinical history or shown in CT or MR imaging studies within the previous year and reported as cerebrovascular disease. |
| **Atrial fibrillation** | Indicate if the previous history describes permanent or chronic atrial fibrillation or an electrocardiogram performed within the previous year shows atrial fibrillation and this continues to be present. |
| **Heart valve disease** | Indicate if the patient has any type of clinically significant heart valve disease according to an ultrasound or hemodynamic study reported in the previous clinical history. |
| **Peripheral vascular disease** | Indicate if the patient has peripheral artery disease in either the lower extremities or carotid artery, and if the patient is receiving specific treatment, has undergone specific surgery (by-pass of lower extremities, endarterectomy, etc.) or there is a previous history of an ankle brachial index <0.90. |
| **Chronic obstructive pulmonary disease** | Indicate if the patient is diagnosed with chronic obstructive pulmonary disease because this is shown under previous clinical history, has undergone a spirometry test which was not normal or the patient is receiving specific treatment |
| **Dementia** | Indicate if the patient has dementia or cognitive deterioration or is receiving specific treatment. |
| **Neoplasia** | Indicate if the clinical history describes the presence of any type of cancer of any grade at present or in the past independently of the current status (active, cured, in complete remission, with or without treatment, etc.). |
| **Liver Cirrhosis** | Indicate if the patient is diagnosed with cirrhosis independently of the etiology or stage or is if receiving specific treatment. |
| **Prior episode of heart failure** | Indicate if the patient has heart failure, is receiving specific treatment or the clinical history reports previous episodes of AHF. |
| **BASELINE STATUS** | |
| **Cardiorespiratory class** | Indicate the functional grade of basal dyspnea (within the 15 days prior to the exacerbation episode) of the patient according to the New York Heart Association (NYHA) scale. Class I: No limitation in physical activity. Routine activity does not cause fatigue, palpitations, dyspnea or angina-like pain. Class II: Slight limitation in physical activity. Comfortable when resting. Routine activity causes fatigue, palpitations, dyspnea or angina-like pain, Class III: Marked limitation in physical activity. Comfortable while resting. Less than normal physical activity causes fatigue, palpitations, dyspnea or angina-like pain. Class IV: Incapacity to perform any physical activity without discomfort. The symptoms of cardiac insufficiency or angina-like syndrome may be present even when resting. Any physical activity increases the discomfort. |
| **Baseline Barthel index** | Barthel index value of the patient at least 15 days prior to the date seen in the ED. |
| **Left ventricular ejection fraction (LVEF) (%)** | Refers to the last value obtained within the previous 6 months. |
| **CHRONIC TREATMENT AT HOME** | |
| **Any diuretic** | Receiving chronic treatment with diuretics, either loop-diuretics or thiazide diuretics or mineralocorticoid receptor antagonist |
| **Mineralcorticoid receptor antagonist** | Receiving chronic treatment with aldosterone-receptor antagonists |
| **Beta-blocker** | Receiving chronic treatment with beta-blocker |
| **Angiotensin-converter enzyme (ACE) inhibitors or angiotensin-II receptor blocker** | Receiving chronic treatment with ACE inhibitors or angiotensin-II receptor blocker |
| **Digoxin** | Receiving chronic treatment with digoxin |
| **VITAL SIGNS AT EMERGENCY DEPARTMENT ARRIVAL** | |
| **Systolic blood pressure** | Systolic blood pressure (SBP) measured in mmHg of the patient on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care. |
| **Heart rate** | Central heart rate measured as beats per minute of the patient on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care. |
| **Room air pulsioxymetry** | Oxygen saturation expressed as percentage obtained by capillary pulsioxymetry on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care. |
| **BLOOD TESTS AT EMERGENCY DEPARTMENT ARRIVAL** | |
| **Hemoglobin** | In g/dL |
| **Creatinine** | In mg/dL |
| **Sodium** | In mmol/L |
| **Potassium** | In mmol/L |
| **Natriuretic peptides: NT-proBNP** | In pmol/L |
| **Increased troponin** | Yes / No (according to the upper limit for normality provided by the manufacturer) |
| **INTENSIVE TREATMENT AT EMERGENCY DEPARTMENT** | |
| **Morphine** | |

(*continued on next page*)

**Supplemental Table 1** (*continued*)

| | |
|---|---|
| | Receiving treatment with subcutaneous or intravenous morphine in the ED |
| **Intravenous diuretic** | Receiving treatment with intravenous diuretic in the ED. Notes whether the intravenous diuretic is administered in continuous intravenous perfusion. |
| **Intravenous nitroglycerine** | Receiving treatment with intravenous nitrates during the first care given in the ED |
| **Inotropic or vasopressor treatment** | Receiving treatment with inotropic or vasoactive drugs (dopamine, dobutamine, levosimendan, noradrenalin) during the first care given in the ED |
| **Digoxin** | Receiving treatment with intravenous digoxin |
| **Amiodarone** | Receiving treatment with intravenous amiodarone |
| **Severity of the decompensation episode** | |
| The severity of the episode was estimated with the MEESSI scale which classifies the risk of death of a patient with left cardiac insufficiency in the 30 days following presentation to the emergency department based on 13 variables obtained at arrival to the emergency department: age, Barthel index, NYHA respiratory class, systolic blood pressure, respiratory frequency, oxygen saturation, signs of low cardiac output, episode triggered by an acute coronary syndrome, left ventricular hypertrophy in the ECG and NT-proBNP, troponin, creatinine and potassium values. | |
| **Low risk** | Predicted risk of death at 30 days between 0 and 3.9% |
| **Intermediate risk** | Predicted risk of death at 30 days between 3.9% to 14.5% |
| **High risk** | Predicted risk of death at 30 days between 14,7% and 25.7% |
| **Very high risk** | Predicted risk of death at 30 days higher than 25.7% |
| **DISPOSITION** | |
| **Discharged home without hospitalization** | Patient is discharged directly home from the ED without hospital admission. |
| **Hospital admission** | Patient was transferred to an in-hospital ward after ED management, whatever the type (regular, semi-intensive, intensive or coronary care unit) or the specialty (internal medicine, cardiology, short stay unit, geriatric unit) or other (including subacute units). |
| **Length of hospital stay** | Length of time from admission to a hospitalization ward until discharge home, in days |

inhibitors present a 30% reduction in the risk of hospitalization for AHF. There are only a few studies reporting a beneficial effect of RAAS inhibitors in HFpEF, although, as previously commented, many of these studies include patients with a LVEF greater than 40 or 45%, making comparison with our results, which included patients with a LVEF of 50% or greater, difficult. In the PEP-CHF study, perindopril in patients over the age of 70 improved the symptoms and exercise capacity and reduced hospitalizations in the first year, although this was not maintained later (20). Likewise, the CHARM-Preserved study reported that candesartan reduced hospitalizations by 26% (22).

Finally, the increased 1-year mortality of 58% with MRA is of note and contrasts with randomized data such as that from the TOPCAT trial in which there certainly was no increase in mortality (and in fact a reduction in HF hospitalization was observed) (23). However, we believe that three relevant differences between the two cohorts could have remarkably influenced the differences. Patients included in the TOPCAT trial had a median age of 69 years, while in our study it was of 83. Elderly populations are more sensitive to drug-related adverse events, and MRA are particularly poorly tolerated in patients with advanced ages (24). Second, in most cases, TOPCAT recruited HF patients with a stable condition. In our study, patient inclusion (time zero) was at the time of decompensation, and the impact of drugs can be different, particularly with increased adverse events in decompensated patients. Finally, TOPCAT included patients with an ejection fraction from 45% on upwards, and we only included patients with an ejection fraction from 50%. Therefore, MRA should be used with caution in elderly populations with HFpEF, such as that in the present study.

It was of note that our results were obtained in a sample of consecutive patients with AHF, and 60% were women. As women are systematically underrepresented in clinical trials, we believe that our data of a real world scenario complement findings reported in ideal clinical trial scenarios. In these latter scenarios, most of the studies on ANHD in HFpEF have shown neutral or non-conclusive results (14,25,26). With this lack of evidence, treatment of HFpEF is limited to depletive and symptomatic treatment and to the control of associated risk factors. For this reason, the current recommendations of ANHD in HFpEF are weak and some guidelines only suggest treatment with angiotensin receptor antagonists and MRA to reduce hospitalizations for AHF, while always maintaining strict control of potassium levels and renal function (8). Nonetheless, the prescription of ANHD in patients with HFpEF is very frequent and, in general, greater than 60%. There are differences between the most prevalent types of ANHD according to different countries. Thus, while in Spain RAAS inhibitors are more commonly used, in Japan and the USA BB predominate, with the prescription of BB in the USA reaching 80% of HFpEF cases (9,27,28). Some authors believe that this elevated prescription of ANHD in HFpEF is not justified and could potentially generate iatrogenesis, especially in older aged patients who make up most of the patients with HFpEF (29). The results of our study are in line with this hypothesis since, with the exception of the use of RAAS inhibitors alone, we found no benefits with the use of ANHD in general, and, in the specific case of BB, their use could even be deleterious. In fact, differences in 1-year mortality after the AHF episode between treated and untreated patients became more evident after the second year quarter for ANHD taking altogether and for BB and MRA when considered individually.

Along the same line as the studies mentioned previously, our results show that treatment with ANHD is very frequent (70%), especially with BB and RAAS inhibitors, alone or in combination. We do not know the reason why these treatments were prescribed to our patients. It is likely that in part of the patients the treatment was not clearly indicated since the ANHD in patients receiving them as chronic treatment were withdrawn after discharge for the episode of AHF in 20% of the cases. However, in many cases their prescription would have been indicated to control associated risk factors, especially hypertension and ischemic cardiomyopathy, which were present in 87.4% and 26.9% of the patients with ANHD, respectively. Treatment of chronic hypertension is the principal preventive factor for the development of HFpEF, and therefore aggressive treatment to maintain the control of blood pressure is strongly recommended (30). Among ANHD, both RAAS inhibitors and BB are therapeutic options for the control of hypertension in HFpEF (with level of evidence: C, class IIb), although the latter are less effective in the control of hypertension and, in view of our results, have a potential deleterious effect on HFpEF itself. Therefore, although ANHD in general are not indicated in the treatment of HFpEF, if it is necessary to control hypertension, treatment with RAAS inhibitors rather than BB should be prioritized. Nonetheless, studies are needed that are specifically designed to demonstrate this choice in patients with HFpEF as defined in the current guidelines; that is, those with a LVEF greater than or equal to 50%.

### 4.1. Limitations

The main limitation of this study is we do not know the reasons for the prescription of ANHD when these are prescribed as chronic medication (pre-decompensation) and at discharge (post-decompensation). This makes it difficult to know whether ANHD are indicated with the aim of controlling a risk factor such as hypertension or if, to the contrary, ANHD are not indicated. Along the same line, we do not know why

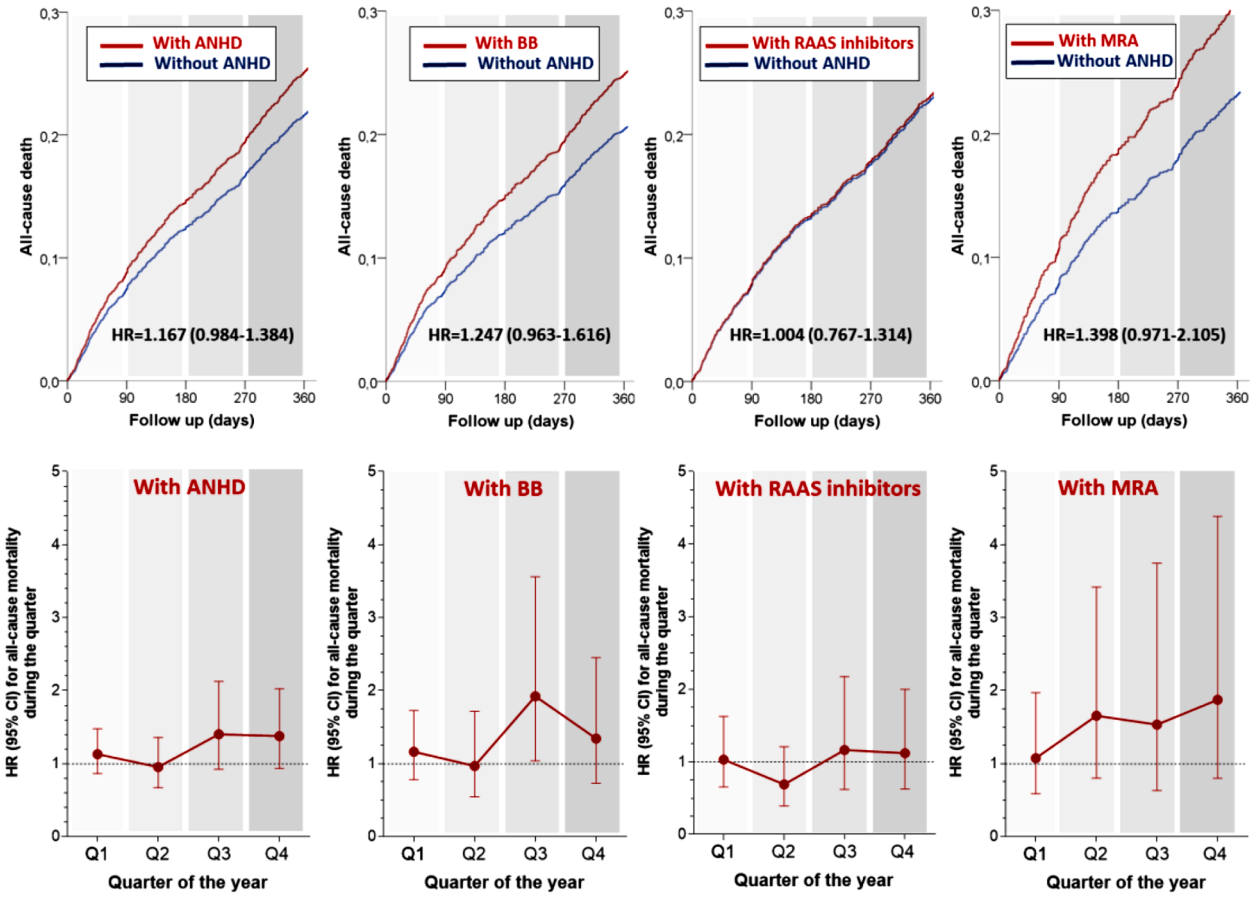



**Fig. 4.** Analysis of adjusted associations between antineurohormonal drugs (whichever or by individual drug class) and 1-year all-cause mortality, during the whole time period (up) and by year quarter (down).
ANHD: antineurohormonal drugs; ED: emergency department; BB: bet-blockers; RAAS: renin-angiotensin-aldosterone; MRA: mineralcorticosteroid-receptor antagonist.

ANHD withdrawn or introduced at discharge, and as mentioned previously, this occurred in an elevated percentage of cases (20% in both groups). Secondly, we do not know if the ANHD doses were correct or were up-titrated to the maximum dose tolerated, although doses lower than maximum titration may also be beneficial for patients (31). Thirdly, we did not perform a follow-up of the potential modifications in treatment during the 90 days after discharge and, in turn, do not know the degree of patient compliance. Fourth, as in every observational study, causal relationships cannot be inferred. Therefore, the results of the current analysis are limited by the retrospective design, potentially including bias by treatment indication, and should be considered as hypothesis generating. In this sense, it was of note that we only recorded one ejection fraction per patient (the most recent in the 6 months previous to decompensation). Therefore, we cannot rule out that some patients may have transitioned from HFpEF to HFrEF, or from HFrEF to HFpEF. In this latter scenario, patients with previous recording of HFrEF should have been considered as HFrEF (or excluded from the present study) even with current normal EF, but we were not able to discriminate this situation and this imposes an additional limitation. Fifth, there was no sample size calculation, and this could have influenced the lack of statistical significance in some comparisons (beta-error). Sixth, the patients came from a nationwide cohort with a universal public health care system, and external validation might be needed to confirm their generalizability. For example, Spanish EDs are able to provide observation, which is not the rule in other countries, and this can influence the percentage of patients who are directly sent home from the ED, without hospitalization, and their prognosis (32). Seventh, our study included a high percentage of elderly AHF patients in whom frailty and dependence are frequent, and are two factors strongly related to mortality (13,33). Eighth, this was real life cohort without any planned intervention, and there could have been differences in physician strategies of ANHD use, not only in terms of indication, but also in terms of the initial doses and up-titration strategies.

## 5. Conclusion

An elevated percentage of patients with HFpEF are treated with ANHD at discharge (70%) with no clear indication, although this could be related to the control of associated factors such as AHT or ischemic cardiomyopathy. Alternatively, some cases could represent incorrect interpretation of the current clinical practice guidelines. Whatever the cause leading to ANHD use, it does not have an impact on mortality or hospitalization, but these drugs are related to an increase in ED revisit for AHF. Among ANHD, RAAS inhibitors could introduce some benefits in the short-term, especially for reducing the risk of hospitalization due to a new AHF episode. However, as our data come from a retrospective analysis of a real world registry, the presence of limited adjustment, residual confounders, lack of information of alternative indications to treatment or no verification of the actual compliance (among others) preclude making firm conclusions until further large international studies verify or refute them.

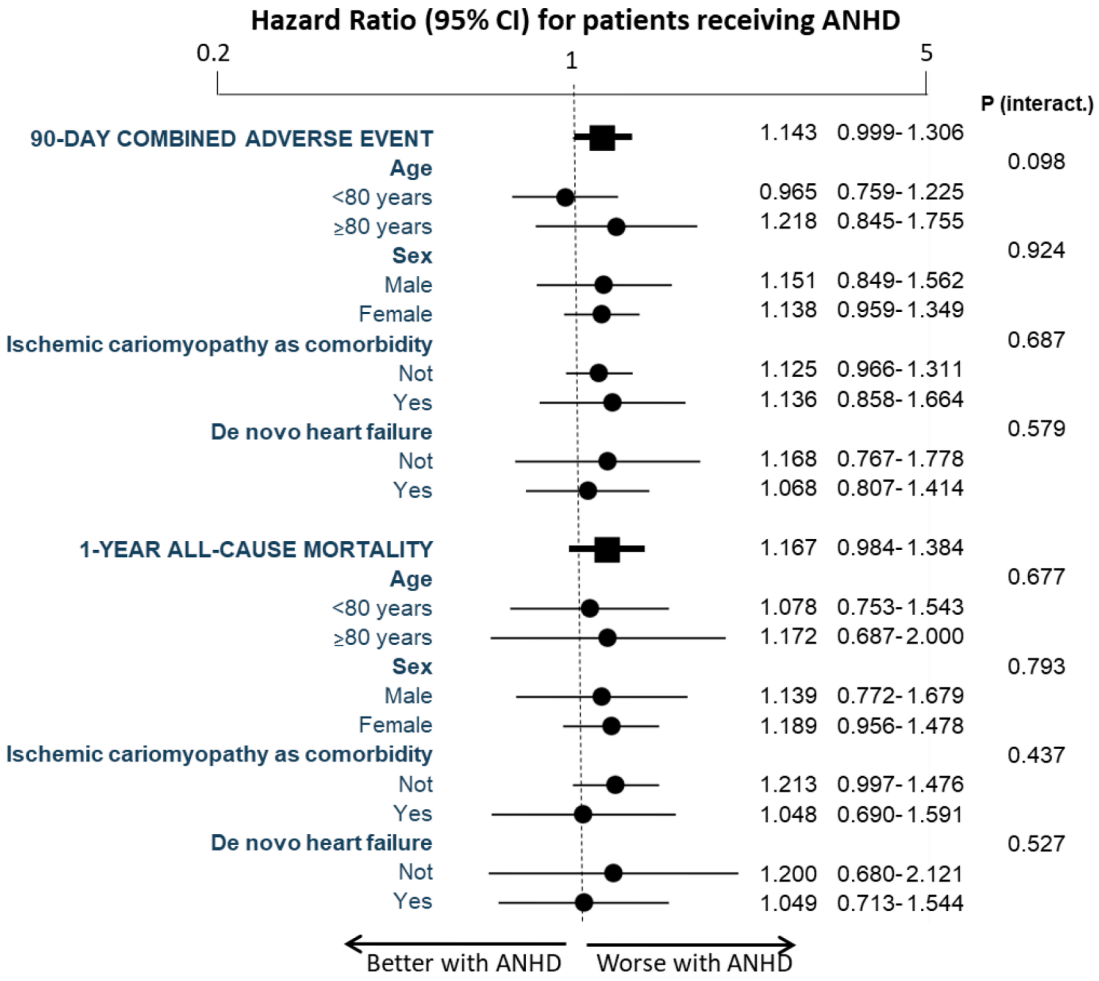



**Fig. 5.** Results of subgroup analyses (according age, sex, ischemic cardiomyopathy and *de novo* heart failure) for the co-primary endpoints
ANHD: antineurohormonal drugs;

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**Appendix 1**

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