Short-term outcomes by chronic betablocker treatment in patients presenting to emergency departments with acute heart failure. BB-EAHFE.

Javier Jacob[1], Antoni Haro[1], Josep Tost[2], Xavier Rossello[3], Pere Llorens[4], Pablo Herrero[5], Francisco Javier Martín-Sánchez[6], Víctor Gil[7], María Luisa López-Grima[8], Javier Millán[9], Alfons Aguirre[10], José Manuel Garrido[11], Rafael Calvo-Rodríguez[12], Enrique Pérez-Llantada[13], José Andrés Sánchez-Nicolás[14], María Mir[15], Esther Rodríguez-Adrada[16], Marta Fuentes-De Frutos[17], Alex Roset[1], Òscar Miró[7] ; on behalf of the ICA-SEMES Research Group.

[1] Emergency Department, Hospital Universitari de Bellvitge. Institute of Biomedical Research of Bellvitge (IDIBELL). University of Barcelona (UB). L'Hospitalet de Llobregat, Barcelona. Spain.

[2] Emergency Department, Consorci Hospitalari de Terrassa, Barcelona. Spain.

[3] Cardiology Department, Health Research Institute of the Balearic Islands (IdISBa), Hospital Universitari Son Espases, Palma, Spain.

[4] Emergency Department, Short Stay Unit and Hospital at Home, Hospital General de Alicante, Instituto de Investigación Sanitaria y Biómedica de Alicante (ISABIAL), Miguel Hernández University, Alicante. Spain.

[5] Emergency Department, Hospital Central Asturias, Oviedo. Spain.

[6] Emergency Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid. Spain.

[7] Emergency Department, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona. Spain.

[8] Emergency Department, Hospital Doctor Peset, Valencia. Spain.

[9] Emergency Department, Hospital Universitario La Fe, Valencia. Spain.

[10] Emergency Department, Hospital del Mar, Barcelona. Spain.

[11] Emergency Department, Hospital Virgen de la Macarena, Sevilla. Spain.

[12] Emergency Department, Hospital Reina Sofía de Córdoba, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba. Spain.

[13] Emergency Department, Hospital Marqués de Valdecilla, Santander. Spain.

[14] Emergency Department, Hospital Reina Sofía, Murcia. Spain.

[15] Emergency Department, Hospital Infanta Leonor, Madrid. Spain.

[16] Emergency Department, Hospital Rey Juan Carlos, Móstoles, Madrid. Spain.

[17] Emergency Department, Hospital Universitario de Salamanca. Spain.

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Corresponding author: Dr. Javier Jacob. Feixa Llarga s/n. L'Hospitalet de Llobregat. 08907. Barcelona.

Email: jjacob@bellvitgehospital.cat

Telefon: 93.227.98.33

Investigators of the ICA-SEMES (Research group on Acute Heart Failure of the Spanish Society of Emergency Medicine): Marta Fuentes, Cristina Gil (Hospital Universitario de Salamanca), Héctor Alonso, Enrique Pérez-Llantada (Hospital Marqués de Valdecilla de Santander), Francisco Javier Martín-Sánchez, Guillermo Llopis García, Mar Suárez Cadenas (Hospital Clínico San Carlos de Madrid), Òscar Miró, Víctor Gil, Rosa Escoda, Sira Aguiló, Carolina Sánchez (Hospital Clínic de Barcelona), Javier Millán (Hospital Politénic La Fe de Valencia), José Pavón, Nayra Cabrera González (Hospital Dr. Negrín de Las Palmas de Gran Canaria), Antonio Noval (Hospital Insular de Las Palmas de Gran Canaria), Rafael Calvo Rodríguez, Juan Antonio Vega Reyes (Hospital Reina Sofía de Córdoba), María Luisa López-Grima, Amparo Valero, María Ángeles Juan (Hospital Dr. Peset de Valencia), Alfons Aguirre, Maria Angels Pedragosa, Silvia Mínguez Masó (Hospital del Mar de Barcelona), María Isabel Alonso, Francisco Ruiz (Hospital de Valme de Sevilla), José Miguel Franco (Hospital Miguel Servet de Zaragoza), Ana Belén Mecina (Hospital de Alcorcón de Madrid), Josep Tost, Marta Berenguer, Ruxandra Donea (Consorci Sanitari de Terrassa), Susana Sánchez Ramón, Virginia Carbajosa Rodríguez (Hospital Universitario Rio Hortega de Valladolid), Pascual Piñera, José Andrés Sánchez Nicolás, Paula Lazaro Aragües (Hospital Reina Sofía de Murcia), Raquel Torres Garate (Hospital Severo Ochoa de Madrid), Aitor Alquézar-Arbé, Miguel Alberto Rizzi, Sergio Herrera (Hospital de la Santa Creu y Sant Pau de Barcelona), Javier Jacob, Alex Roset, Irene Cabello, Antonio Haro (Hospital Universitari de Bellvitge de Barcelona), Fernando Richard, José María Álvarez Pérez, María Pilar López Diez (Hospital Universitario de Burgos), Pablo Herrero Puente, Joaquín Vázquez Álvarez, Belén Prieto García, María García García, Marta Sánchez González (Hospital Universitario Central de Asturias de Oviedo), Pere Llorens, Inmaculada Jiménez, Néstor Hernández , Benjamín Brouzet, Begoña Espinosa, Adriana Gil, Francisca Molina, Tamara García, María Dolores Jodar (Hospital General Universitario de Alicante), Juan Antonio Andueza (Hospital General Universitario Gregorio Marañón de Madrid), Rodolfo Romero (Hospital Universitario de Getafe de Madrid), Martín Ruíz, Roberto Calvache (Hospital de Henares de Madrid), María Teresa Lorca Serralta, Luis Ernesto Calderón Jave (Hospital del Tajo de Madrid), Beatriz Amores Arriaga, Beatriz Sierra Bergua (Hospital Clínico Lozano Blesa de Zaragoza), Enrique Martín Mojarro, Brigitte Silvana Alarcón Jiménez (Hospital Sant Pau i Santa Tecla de Tarragona), Lisette Travería Bécquer, Guillermo Burillo (Hospital Universitario de Canarias de Tenerife), Lluís Llauger García, Gerard Corominas LaSalle. (Hospital Universitari de Vic de Barcelona), Carmen Agüera Urbano, Ana Belén García Soto, Elisa Delgado Padial (Hospital Costa del Sol de Marbella de Málaga), Ester Soy Ferrer, María Adroher Múñoz (Hospital Josep Trueta de Girona). José Manuel Garrido (Hospital Virgen Macarena de Sevilla), Francisco Javier Lucas-Imbernón (Hospital General Universitario de Albacete), Rut Gaya (Hospital Juan XXIII de Tarragona), Carlos Bibiano, María Mir, Beatriz Rodríguez (Hospital Universitario Infanta Leonor de Madrid), José Luis Carballo (Complejo Hospitalario Universitario de Ourense), Esther Rodríguez-Adrada, Belén Rodríguez Miranda, Monika Vicente Martín (Hospital Rey Juan Carlos de Móstoles de Madrid). Pere Coma Casanova, Joan Espinach Alvarós (Hospital San Joan de Deu de Martorell, Barcelona).

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ABSTRACT

Objective: To evaluate the association between chronic treatment with betablockers (BB) and the severity of decompensation and short-term outcomes of patients with acute heart failure (AHF).

Methods: We consecutively included all patients presenting with AHF to 45 Spanish emergency departments (ED) during six different time-periods between 2007 and 2018. Patients were stratified according to whether they were on chronic treatment with BB at the time of ED consultation. Those receiving BB were compared (adjusted odds ratio -OR- with 95% confidence interval -CI-) with those not receiving BB group in terms of in-hospital and 7-day all-cause mortality, need for hospitalisation and prolonged length of stay (≥7 days).

Results: Among the 17,923 recruited patients (median age: 80 years; 56% women), 7,795 (43%) were on chronic treatment with BB. Based on the MEESSI-AHF risk score, those on BB were at lower risk. In-hospital mortality was observed in 1,310 patients (7.4%), 7-day mortality in 765 (4.3%), need for hospitalisation in 13,428 (75.0%), and prolonged length of stay (43.3%). After adjustment for confounding, those on chronic BB were at lower risk for in-hospital all-cause mortality (OR=0.85, 95% CI=0.79-0.92, p<0.001); 7-day all-cause mortality (OR=0.77, 95% CI=0.70-0.85, p<0.001); need for hospitalisation (OR=0.89, 95% CI=0.85-0.94, p<0.001); prolonged length of stay (OR=0.90, 95% CI=0.86-0.94, p<0.001). A propensity matching approach yielded consistent findings.

Conclusion: In patients presenting to emergency departments with acute heart failure, those on BB had better short-term outcomes than those not receiving BB.

Introduction

Heart failure (HF) is a clinical syndrome with symptoms and/or signs caused by a structural heart defect and/or functional anomaly that is confirmed by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion **(1, 2)**. This disease is a global health problem with a prevalence in the general population of around 1-2%, and it is the first cause of hospitalisation, especially in persons over the age of 65 years **(3-5)**. HF is associated with high healthcare cost, particularly during the episodes of acute heart failure (AHF) requiring hospitalisation. The prognosis of HF is poor is many cases, since mortality is about 50% at 5 years. Therefore, it is interesting to investigate the existence of variables that are associated with a better prognosis during hospitalization. Over the last decades the mortality and need for admission of patients with left ventricular fraction (LVEF) ≤40% (HFrEF) have been increasingly reduced due to the implementation of treatments that modulate the activation of the sympathetic nervous and renin-angiotensin-aldosterone (RAAS) systems. These drugs include betablockers (BB) **(1)**. BB were originally developed to control angina and hypertension **(6, 7)**. In the complex pathophysiology of HF, with an increase in sympathetic adrenergic activity, randomized clinical trials showed that BB reduced mortality **(8-16)**. At present, the use of BBs in patients with HFrEF has a class of recommendation I, with a level of evidence A, though this applies to those which have demonstrated benefits in clinical trials: bisoprolol, carvedilol, metoprolol succinate and nebivolol **(1)**. BB have also shown to improve the functional class, exercise capacity symptoms and quality of life **(16)**. Retrospective analyses show that discontinuation or dose reduction of beta-blocker therapy during an AHF hospitalization is associated with poor clinical outcomes **(1, 17)**. Likewise, patients not taking BB and who are haemodynamically stable can cautiously initiate BB at low doses **(1, 16-19)**. In addition, treatment with BB plays an important role in the management of other cardiovascular diseases, and they are usually used for their anti-ischaemic, anti-arrhythmic and anti-hypertensive properties **(20)**. For all these reasons, many patients attending the emergency departments (ED) for an episode of AHF are on chronic BBs, even those patients with a preserved LVEF ≥50% (HFpEF) or mildly reduced LVEF 41-49% (HFmrEF). During an episode of HF there is an increase in neurohormonal activity with relevant consequences on the outcome of the episode **(21)**. Some studies have described that starting BB during hospitalization for AHF improves outcomes **(22, 23)**. However, there is little evidence in clinical practice if taking BB before the AHF episode improves the prognosis of this episode **(22, 24)**. We hypothesize that chronic treatment with BB provides a cardioprotective effect during an episode of AHF, producing a less severe clinical presentation and better short-term outcomes.

Methods

Setting

The present study is a retrospective analysis of the data from the EAHFE (Epidemiology of Acute Heart Failure in Spanish Emergency Departments) registry. This registry was initiated in 2007 and is carried out approximately every two years over a period of one or two months, consecutively recruiting patients with AHF at the ED. 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, enrolling a total of 18,370 AHF patients. Details of patient inclusion have been extensively reported elsewhere **(25-28)**. The data collection methodology has been the same in all the recruitment periods and has been already published**.** Only those patients with an ongoing ST-elevation myocardial infarction (STEMI) were excluded from the study.

Study design and variables recorded

This analysis was limited to patients with information related to chronic treatment with BB. Among those receiving BB, two subgroups were made: those receiving heart failure recommended (HFR) BB (bisoprolol, carvedilol, metoprolol or nebivolol), and those receiving other type of BB (classified as non-HFR). Within the HFR BB group, two more subgroups were defined based on the dose of BB received. A reduced dose was defined as a dose < 50% the total dose recommended by the guidelines (bisoprolol < 5mg once daily, carvedilol < 12.5mg twice daily, metoprolol <100mg once daily and nebivolol <5mg once daily). A full dose was defined as a dose greater than or equal to these cut-offs **(1).**

Forty-four independent variables were collected. These included demographic data (age, sex), comorbidities (arterial hypertension, diabetes mellitus, dyslipaemia, ischaemic heart disease, chronic renal failure, cerebrovascular accident, atrial fibrillation, peripheral artery disease, heart valve disease, chronic obstructive pulmonary disease, previous heart failure), basal status (Barthel index,–New York Heart Association -NYHA - class, LVEF), baseline treatment (loop diuretics, BB [type and dose], ACEi or ARB, MRAs, calcium channel blockers, digoxin, amiodarone, nitrates), data of the acute episode (dyspnoea, oedema, elevated jugular venous pressure, symptoms of low cardiac output, oxygen saturation, systolic blood pressure -SBP-, heart rate -HR-, natremia, estimated glomerular filtration rate -eGFR- and NT-proBNP), precipitating factor (atrial fibrillation, anaemia, hypertensive emergency, non ST-elevation acute coronary syndrome, management in the ED (oxygen therapy, diuretics, intravenous nitrates, inotropic or vasopressors, morphine, non-invasive ventilation), as well as the estimated prognosis provide by the MEESSI-AHF risk score. The MEESSI-AHF risk 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 and creatinine levels) **(27)**. Several studies have demonstrated that the MEESSI score adequately stratifies the risk of death during the following 30 days after ED presentation **(27, 29)**.

Outcomes

We defined the primary endpoint as all-cause in-hospital mortality. Secondary endpoints were 7-day all-cause mortality, hospitalisation, and long length of stay in hospitalised patients. Based on the median hospital stay for patients with AHF observed in previous studies by our group, prolonged hospitalisation was considered if patients remained hospitalised more than 7 days **(30)**. For all outcomes, the follow up started at the time of ED admission and ended at hospital discharge or death.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD), or median and interquartile range (IQR) if not normally distributed, whereas categorical variables are presented as frequencies and percentages. Comparisons of continuous variables were carried out using the t test, or the Mann–Whitney non-parametric test for non-normally distributed variables (checked through the Kolmogorov–Smirnov test). The chi-square test (for trend, when needed) was used for comparing categorical variables. Continuous variables were dichotomized with cut-offs with prognostic implications based on previous studies (Barthel index<60 points, O2 saturation ≤90%, SBP ≤100 mmHg, HR ≤100 beats per minute, eGFR <60 ml/min/1.73m2, NT-proBNP ≥5000 pmol/L, LVEF ≤40%, sodium ≤135mmol/L). Odds ratios (OR) with their 95% confidence intervals (CI) were used to estimate associations between the exposure (BB vs. noBB) and outcomes. Estimates were obtained from unadjusted and adjusted multivariate logistic models by entering all the variables showing a significant association in the univariate analyses **(31, 32)**. A multiple imputation technique generating five datasets was used to address missing values of adjusted model. Subsequently, two types of analysis were carried out. Stratified analyses according to: (a) type of BB (heart failure recommended /non- heart failure recommended); (b) dose of BB (reduced/full dose); and (c) LVEF ≤40%. Sensitivity analyses including only: (a) patients with natriuretic peptides (certainty of diagnosis), (b) only hospitalised patients (clinically significant episode), (c) BB maintained in the ED or hospital (certainty of BB treatment); and (d) previous diagnosis of AHF (BB is probably given in the context of HF). To provide further certainty about the findings, a propensity score marching was performed using the same covariates used for the adjusted regression-based approach. Individuals with a difference in the probability obtained < 0.05 were matched using a 1:1 ratio. Statistical significance was set at a p value less than 0.05. All analyses were performed using the SPSS, version 24.0 (SPSS Inc Chicago, USA).

Ethical aspects

The EAHFE Registry was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain). Due to the non-interventional design of the registry, Spanish

legislation allows central Ethical Committee approval, accompanied by notification to the local Ethical Committees. At admission, all participating patients gave informed consent (written 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.

Results

Of the 18,370 patients included in the EAHFE registry, data regarding chronic BB treatment was available in 17,923 (97.6%), which was our study populations **(Figure 1)**. The characteristics of the patients not included (n=447) are described in the **supplementary material table 1.** The overall mean (SD) age was 80.4 (10.2) years, and 55.7% were women. Chronic BB treatment was taken by 7,795 (43.5%) patients. The univariate analysis comparing the noBB and BB cohorts showed differences in 33 of the 44 variables **(Table 1)**. Patients receiving BB were younger, more often were women, and had more comorbidities (except for chronic obstructive pulmonary disease). They received less frequently calcium channel antagonists and digoxin, and more received more often diuretics, ACE inhibitors (or ARB), and MRA. They also had less frequently a Barthel index <60 points, and more frequently a LVEF≤40%. Regarding the acute episode, patients with BB presented a different clinical picture with a greater presence of dyspnoea but lower O2 saturation ≤ 90% and oedema. In comparison to those not receiving BB, there was a higher percentage of patients with SBP ≤ 100 mmHg and HR ≤ 100 bpm among those on chronic BB. They also had a higher percentage of patients in the category low or intermediate MEESSI risk score (i.e., better estimated prognosis at 30 days). In relation to the treatment received in the ED, patients on BB were more frequently under intravenous nitrates and less frequently received oxygen therapy.

In-hospital all-cause mortality was observed in 1,310 patients (7.4%): 497 (6.4%) in the BB group, and 813 (8.1%) in the noBB group. After adjustment for potential confounding, the adjusted OR (aOR) was 0.84 (95% CI 0.78-0.91), p<0.001. For the remaining endpoints, the findings pointed towards the same direction, favouring those on chronic BB. For 7-day mortality, the aOR was 0.78 (95% CI 0.71-0.86), p<0.001; whereas for need for hospitalisation was 0.87 (95% CI 0.84-0.92), p<0.001; and for prolonged length of stay was 0.89 (95% CI 0.85-0.92), p<0.001. The propensity score matching yielded consistent findings **(table 2)**. Sensitivity analyses **(Table 3)** performed using only patients with AHF confirmed with elevated natriuretic peptides, patients requiring hospitalisation, patients in whom BB treatment was maintained during hospital stay, and patients with a previous history of HF, showed consistent findings as well. The stratified analysis **(Table 4)** showed significant differences in terms of in-hospital all-cause mortality, when comparing HFR BB versus noBB, and full versus reduced dose BB. The analysis by LVEF categories **(Table 5)** showed differences in all-cause in-hospital mortality in patients with LVEF ≤ 40% and LVEF ≥ 50% (the larger groups), but not for LVEF 41-49% (the smallest group, with less than 1,000 patients).

Discussion

In patients presenting to the ED with AHF, there was an association between chronic treatment with BB and a lower in-hospital mortality, 7-day all-cause mortality, need for hospitalisation and prolonged length of stay. These differences remained after the adjustment for the differences in baseline characteristics, presentation of the acute episode and treatment in the ED. These results confirm our hypothesis that chronic BB have a positive impact on short-term outcomes and less sever presentation during an episode of AHF.

The pathophysiology of AHF is complex since an increase in neurohormonal activation is produced during an episode of AHF (i.e., sympathetic and renin-angiotensin-aldosterone axis raised activity). Activation of the sympathetic system increases systolic volume and induces peripheral vasoconstriction for maintaining arterial perfusion pressure. An episode of AHF is a period of high vulnerability for patients. There is an increase in end-diastolic filling pressures, changes in arterial pressure, pulmonary and systemic congestion, an increase in contractility which can produce myocardial ischemia and troponin release, increased levels of markers of myocardial stress, such as natriuretic peptides, an increase in inflammatory markers, and renal function impairment **(21, 26, 33-39)**. BB have multiple effects through the inhibition of sympathetic activation, and β1 receptor blockade reduces contractibility, relaxation, HR, and excitability **(33)**. In our study, those patients on chronic BB had a different presentation (e.g., SBP ≤100 mmHg and a HR ≤100 bpm were more frequent in these patients). It is reasonable to consider that patients receiving treatment with BB have less activation of the sympathetic system and this may be associated with a better short-term outcome. It is already known that HR is an important target for the treatment of HF in patients in sinus rhythm, and that the use of BB or ivabradine provides greater benefits based on better control of the HR **(40-42)**.

Our findings are of particular relevance when they are evaluated in the light of the several unsuccessful attempts to improve the prognosis of patients with AHF using new treatments. The use of nesiritide showed major improvement of dyspnoea but the effect was not clinically significant, and there were no differences in the all-cause 30-day mortality rates or in the rates of re-admission for AHF **(43)**. Ularitide which had shown clinical and haemodynamic benefits in two previous trials, showed favourable physiological effects, but short-term treatment did not reduce cardiovascular-related mortality and it was not associated with significant clinical improvement **(44)**. Serelaxin did not result in a lower incidence of death by cardiovascular causes at 180 days or worsening of HF at 5 days compared to placebo in patients with AHF **(45)**. Other studies have shown an association between not receiving BB and a worse prognosis during an episode of AHF in terms of higher mortality and longer length of hospital stay. Moreover, the initiation of BB treatment during an episode of AHF with hospitalization has been associated with a reduction in in-hospital mortality, both cardiovascular and non-cardiovascular **(22-24)**. Our results suggest that chronic BB treatment is yet cardioprotective when the patient presents an exacerbation.

On top of the primary findings regarding inhospital mortality, our study also shows that there was an association between chronic BB treatment and a lower need for hospitalisation and a shorter hospital stay. Previous studies have described a reduction in hospitalisation among patients receiving BB for the treatment of HF **(1, 16)**. The group of patients receiving BB presented a greater percentage of patients in low and intermediate MEESSI-AHF categories (i.e., lower risk patients compared to those not receiving BB). These patients require fewer hospital admissions due their reduced risk and, in the case of admission, the stay is shorter.

Our study evaluated patients receiving chronic BB treatment without taking into account early use of BB treatment in the acute phase in patients included in the noBB group. Nonetheless, previous studies have shown that both maintaining chronic BB treatment during hospitalisation and initiating BB during admission when haemodynamic stability is achieved are associated with better long-term outcomes, and this is currently recommended in the clinical practice guidelines **(1, 17-19)**. Our findings might support the need to initiating BB treatment in patients with AHF.

When the results are assessed by LVEF category, we found a statistically significant association between receiving BB and better outcomes for HFrEF and HFpEF patients, but not for HFmrEF. This association was not found in the propensity matching analysis. Of note, caution should be exercised when groups are small (e.g., HFmrEF) or become smaller due to the characteristics of the analysis (e.g., unpaired patients are excluded from propensity score matching approaches). In any case, we cannot confirm these findings are consistent across the whole range of HF patients.

Study limitations

The present study has several limitations. Since it was a prospective observational study and was not randomised, we cannot make inferences about causal effects, but rather associations. In spite of adjusting for 30 covariate, some remaining residual confounding might bias our findings **(31, 32)**. Moreover, there is a possibility of bias by indication for BB treatment. Although all the patients had AHF, we did not collect the initial indication for which the patients received BB. We do not have information about the reason to receive (or not) the BB. Another limitation might be the unknown previous duration of treatment with BB. However, it is known that the BB treatment is effective from the beginning, at low doses, so we are sceptical about whether this information might have changed our findings. Our study included a high percentage of patients without a recent determination of the LVEF; however, a multiple imputation analysis was performed to address this issue. The benefits of control of the HR with BB treatment have been demonstrated in patients in sinus rhythm but not in patients with atrial fibrillation. We did not perform an analysis of this type of patients, although they were more frequent in the BB group. Our study included an older AHF population than some other populations included in studies limited to patients hospitalised in cardiology departments. As frailty and dependence are frequent in elder patients and these are two factors are strongly related to mortality **(46, 47)**, our results have to be confirmed in other populations of AHF patients. Finally, EAHFE registry is a nationwide cohort and therefore caution

must be taken when extrapolating our results to other countries, as type and organization characteristics of every national health care system can impact on some of the outcomes **(48, 49).**

Conclusion

There is an association between chronic treatment with BB and reduction of short-term adverse events in patients presenting an episode of AHF in the ED.

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Table 1. Patient characteristics and comparison between groups: No betablockers versus betablockers.

	Total (n=17923)	No betablockers (n=10128)	Betablockers (n=7795)	Missing values	p value§
Epidemiologic variables					
Age (years), mean (SD)	80.4 (10.2)	81.3 (10.1)	79.3 (10.1)	26 (0.1)	<0.001
Female sex, n (%)	9953 (55.7)	5702 (56.4)	4251 (54.7)	43 (0.2)	0.025
Personal history (n, %)					
Arterial hypertension	14950 (83.6)	8237 (81.6)	6713 (86.2)	39 (0.2)	<0.001
Diabetes mellitus	7524 (42.1)	3917 (38.8)	3607 (46.3)	41 (0.2)	<0.001
Dyslipaemia	7881 (44.1)	3996 (39.6)	3885 (49.9)	40 (0.2)	<0.001
Ischaemic heart disease	5082 (28.4)	2028 (20.1)	3054 (39.2)	41 (0.2)	<0.001
Chronic renal failure	4664 (26.1)	2394 (23.7)	2270 (29.2)	38 (0.2)	<0.001
Cerebrovascular accident	2234 (12.5)	1203 (11.9)	1031 (13.2)	40 (0.2)	0.008
Atrial fibrillation	8851 (49.5)	4471 (44.3)	4380 (56.3)	40 (0.2)	<0.001
Peripheral artery disease	1626 (9.1)	809 (8.0)	817 (10.5)	42 (0.2)	<0.001
Heart value disease	4566 (25.5)	2387 (23.6)	2179 (28.0)	39 (0.2)	<0.001
COPD	4181 (23.4)	2729 (27.0)	1452 (18.7)	48 (0.2)	<0.001
Previous heart failure	10663 (64.1)	5504 (59.1)	5159 (70.5)	1294 (7.2)	<0.001
Basal status (n, %)					
Barthel index < 60 points	3079 (19.0)	1872 (20.3)	1207 (17.3)	1726 (9.6)	<0.001
NYHA class III–IV	4211 (24.9)	2365 (24.8)	1846 (24.9)	995 (5.6)	0.853
Reduced LVEF (≤40%)	2267 (24.1)	821 (18.3)	1446 (29.5)	8533 (47.6)	<0.001
Baseline treatment (n, %)					
Loop diuretics	11860 (66.2)	6246 (61.7)	5614 (72.1)	7 (0.0)	<0.001
ACE inhibitors or ARB	10040 (56.0)	5441 (53.7)	4599 (59.0)	7 (0.0)	<0.001
MRB	2956 (16.5)	1360 (13.4)	1596 (20.5)	5 (0.0)	<0.001
Calcium channel blockers	4713 (26.3)	2994 (29.6)	1719 (22.1)	7 (0.0)	<0.001
Digoxin	2670 (14.9)	1631 (16.1)	1039 (13.3)	17 (0.1)	<0.001
Amiodarone	995 (5.6)	513 (5.1)	482 (6.2)	11 (0.1)	0.001
Nitrates	2978 (16.6)	1326 (13.1)	1652 (21.2)	8 (0.0)	<0.001
Data of the acute episode (n, %)					
Dyspnoea	16167 (90.5)	9068 (89.8)	7099 (91.4)	54 (0.3)	<0.001
Oedema	12185 (68.2)	7020 (69.5)	5165 (66.5)	50 (0.3)	<0.001
Elevated jugular venous pressure	3636 (20.3)	2058 (20.4)	1578 (20.3)	53 (0.3)	0.900
Symptoms of low cardiac output [1]	2766 (17.8)	1549 (18.3)	1217 (17.1)	2378 (13.3)	0.050
O2 saturation ≤ 90%	4774 (27.7)	2941 (30.3)	1833 (24.4)	686 (3.8)	<0.001
SBP ≤ 100 mmHg	1020 (5.8)	526 (5.3)	494 (6.4)	288 (1.6)	0.001
HR ≤ 100 bpm	12613 (72.5)	6885 (70.2)	5728 (75.5)	518 (2.9)	<0.001
Hyponatremia [2]	3899 (22.5)	2215 (22.8)	1684 (22.2)	625 (3.5)	0.330
eGFR < 60 ml/min/1.73m2	9798 (56.0)	5339 (54.2)	4459 (25.5)	415 (2.3)	<0.001
NT-proBNP ≥ 5000 pmol/L	3497 (40.2)	1741 (37.0)	1756 (43.9)	9219 (51.4)	<0.001
Precipitating factors					
Atrial fibrillation	2314 (14.4)	1310 (14.7)	1004 (14.1)	1894 (10.6)	0.295
Anaemia	1088 (6.8)	617 (6.9)	471 (6.6)	1892 (10.6)	0.447
Hypertension	853 (5.3)	435 (4.9)	418 (5.9)	1892 (10.6)	0.005
Non ST segment acute coronary syndrome	415 (2.3)	209 (2.1)	206 (2.7)	129 (0.7)	0.010
Severity of the AHF episode					
MEESSI risk category				8421 (47.0)	0.001*
Low risk	3742 (39.4)	1971 (37.8)	1771 (41.3)		
Intermediate risk	3810 (40.1)	2121 (40.6)	1689 (39.4)		
High risk	1022 (10.8)	581 (11.1)	441 (10.3)		
Very high risk	928 (9.8)	546 (10.5)	382 (8.9)		
Management in the ED (n, %)					
Use of oxygen therapy	12844 (72.3)	7359 (73.3)	5485 (71.1)	170 (0.9)	0.001
Use of diuretics [3]	15501 (87.3)	8760 (87.3)	6741 (87.4)	167 (0.9)	0.854
Use of intravenous nitrates	2472 (13.9)	1336 (13.3)	1136 (14.7)	168 (0.9)	0.007
Use of inotropic or vasopressors	289 (1.7)	147 (1.6)	142 (1.9)	1109 (6.2)	0.115
Use of morphine	937 (6.1)	510 (6.1)	427 (6.0)	2437 (13.6)	0.968
Use of NIV in the ED	1195 (6.7)	682 (6.8)	513 (6.7)	209 (1.2)	0.688

NYHA: New York Heart Association, COPD: chronic obstructive pulmonary disease, LVEF: left ventricle ejection fraction, ACE: angiotensin converter enzyme, ARB: angiotensin receptor blocker, MRB: mineralocorticoid receptor blocker, SBP: systolic blood pressure, HR: heart rate, bpm: beats per minute, STEMI: ST-elevation myocardial infarction, eGFR: estimated glomerular filtration rate, ED: emergency department, NIV: non-invasive ventilation. 1. Symptoms of low cardiac output (cold sweaty extremities, slow

capillary refilling, livedo reticularis and/or mental confusion), 2. Hyponatremia (sodium ≤ 135mmol/L), 3. Intravenous diuretics bolus, infusion, or both. * p-value for the comparison of the four MEESSI risk categories.

§ p-values for the comparison between those on chronic BB and those not receiving chronic BB

Table 2. Comparison of endpoints between groups with OR (95% CI): no betablockers versus betablockers.

	Primary endpoint	**Secondary endpoints**		
	In-hospital all-cause mortality	7-day all-cause mortality	Need for hospitalisation	Prolonged length of stay (≥ 7 days)
Unadjusted	0.78 (0.69-0.87) <0.001	0.78 (0.68-0.91) 0.001	0.86 (0.81-0.93) <0.001	0.90 (0.84-0.96) 0.002
Adjusted* with multiple imputation	0.84 (0.78-0.91) <0.001	0.78 (0.71-0.86) <0.001	0.87 (0.84-0.92) <0.001	0.89 (0.85-0.92) <0.001
Propensity matching * with simple imputation	0.84 (0.70-0.99) 0.045	0.87 (0.70-1.09) 0.235	0.90 (0.81-1.00) 0.052	0.89 (0.80-0.99) 0.029

*Adjusted for: age, male sex, arterial hypertension, diabetes mellitus, dyslipaemia, ischaemic heart disease, chronic renal failure, cerebrovascular accident, atrial fibrillation, peripheral artery disease, heart value disease, chronic obstructive pulmonary disease, previous heart failure, Barthel index < 60 points, reduced left ventricle ejection fraction, baseline treatment loop diuretics, angiotensin converter enzyme inhibitors or angiotensin II receptor blocker, mineralocorticoid receptor blocker, calcium channel blockers, digoxin, amiodarone or nitrates; dyspnoea, oedema, symptoms of low cardiac output in acute episode, O2 saturation ≤ 90%, eGFR < 60 ml/min/1.73m^2, NT-proBNP ≥ 5000 pmol/L, use of oxygen therapy or intravenous nitrates in the emergency department.

OR: odds ratio. CI: confidence interval.

Table 3. Sensitivity analysis with OR (95% CI). Adjusted model (with multiple imputation)*.

	Primary endpoint	**Secondary endpoints**		
	In-hospital all-cause mortality	7-day all-cause mortality	Need for hospitalisation	Prolonged length of stay (≥ 7 days)
Main analysis (n=17923)	0.84 (0.78-0.91) <0.001	0.78 (0.71-0.86) <0.001	0.87 (0.84-0.92) <0.001	0.89 (0.85-0.92) <0.001
Including only patients with AHF confirmed by natriuretic peptides (n=9219)	0.85 (0.78-0.93) 0.001	0.78 (0.70-0.88) <0.001	0.86 (0.81-0.92) <0.001	0.86 (0.81-0.90) <0.001
Including only patients hospitalised after ED care (n=13533)	0.85 (0.79-0.91) <0.001	0.77 (0.70-0.85) <0.001	Not applicable	0.89 (0.85-0.92) <0.001
Including only patients in whom BB were maintained (n=2564)	0.55 (0.42-0.74) <0.001	0.58 (0.39-0.88) 0.009	0.50 (0.41-0.60) <0.001	1.00 (0.86-1.17) 0.985
Including only patients with previous episodes of AHF (n=10663)	0.92 (0.85-0.99) 0.044	0.81 (0.73-0.91) <0.001	0.93 (0.88-0.98) 0.010	0.91 (0.87-0.96) <0.001

OR: odds ratio. CI: confidence interval.

* Adjusted for: age, male sex, arterial hypertension, diabetes mellitus, dyslipaemia, ischaemic heart disease, chronic renal failure, cerebrovascular accident, atrial fibrillation, peripheral artery disease, heart value disease, chronic obstructive pulmonary disease, previous heart failure, Barthel index < 60 points, reduced left ventricle ejection fraction, baseline treatment loop diuretics, angiotensin converter enzyme inhibitors or angiotensin II receptor blocker, mineralocorticoid receptor blocker, calcium channel blockers, digoxin, amiodarone or nitrates; dyspnoea, oedema, symptoms of low cardiac output in acute episode, O2 saturation ≤ 90%, eGFR < 60 ml/min/1.73m2, NT-proBNP ≥ 5000 pmol/L, use of oxygen therapy or intravenous nitrates in the emergency department.

Table 4. Association of betablockers on the endpoints evaluated in the present study. Adjusted model (with multiple imputation)*.

	Adjusted* OR (95%CI); p
In-hospital all-cause mortality (primary endpoint) for betablockers (all) versus no betablockers	0.84 (0.78-0.91); <0.001
According to selectivity	
HFR betablockers versus no betablockers	0.86 (0.80-0.92); <0.001
Non-HFR betablockers versus no betablockers	0.78 (0.68-1.02); 0.078
HFR versus non-HFR betablockers	1.04 (0.84-1.28); 0.747
According to dose	
Full dose HFR betablockers versus no betablockers	0.80 (0.71-0.89); <0.001
Reduced dose HFR betablockers versus no betablockers	0.86 (0.79-0.95); 0.002
Full versus reduced dose HFR betablockers	1.07 (0.95-1.20); 0.276
7-day all-cause mortality for betablockers (all) versus no betablockers	0.78 (0.71-0.86); <0.001
According to selectivity	
HFR betablockers versus no betablockers	0.80 (0.73-0.89); <0.001
Non-HFR betablockers versus no betablockers	0.72 (0.55-0.96); 0.005
HFR versus non-HFR betablockers	1.20 (0.89-1.60); 0.230
According to dose	
Full dose HFR betablockers versus no betablockers	0.75 (0.65-0.86); <0.001
Reduced dose HFR betablockers versus no betablockers	0.80 (0.71-0.90); <0.001
Full versus reduced dose HFR betablockers	1.03 (0.88-1.20); 0.708
Need for hospitalisation for betablockers (all) versus no betablockers	0.87 (0.84-0.92); <0.001
According to selectivity	
HFR betablockers versus no betablockers	0.88 (0.84-0.92); <0.001
Non-HFR betablockers versus no betablockers	0.98 (0.88-1.09); 0.755
HFR versus non-HFR betablockers	0.94 (0.84-1.05); 0.287
According to dose	
Full dose HFR betablockers versus no betablockers	0.83 (0.78-0.88); <0.001
Reduced dose HFR betablockers versus no betablockers	0.88 (0.83-0.94); <0.001
Full versus reduced dose HFR betablockers	1.05 (0.98-1.12); 0.165
Prolonged length of stay (≥ 7 days) for betablockers (all) versus no betablockers	0.89 (0.85-0.92); <0.001
According to selectivity	
HFR betablockers versus no betablockers	0.90 (0.86-0.94); <0.001
Non-HFR betablockers versus no betablockers	0.91 (0.82-1.00); 0.052
HFR versus non-HFR betablockers	1.00 (0.90-1.11); 0.952
According to dose	
Full dose HFR betablockers versus no betablockers	0.91 (0.86-0.97); 0.002
Reduced dose HFR betablockers versus no betablockers	0.82 (0.78-0.87); <0.001
Full versus reduced dose HFR betablockers	0.91 (0.86-0.97); 0.006

*Adjusted for: age, male sex, arterial hypertension, diabetes mellitus, dyslipaemia, ischaemic heart disease, chronic renal failure, cerebrovascular accident, atrial fibrillation, peripheral artery disease, heart value disease, chronic obstructive pulmonary disease, previous heart failure, Barthel index < 60 points, reduced left ventricle ejection fraction, baseline treatment loop diuretics, angiotensin converter enzyme inhibitors or angiotensin II receptor blocker, mineralocorticoid receptor blocker, calcium channel blockers, digoxin, amiodarone or nitrates; dyspnoea, oedema, symptoms of low cardiac output in acute episode, O2 saturation ≤ 90%, eGFR < 60 ml/min/1.73m^2, NT-proBNP ≥ 5000 pmol/L, use of oxygen therapy or intravenous nitrates in the emergency department.

OR: odds ratio. CI: confidence interval. HFR: heart failure recommended.

Table 5. Comparison of endpoints between groups, based on the LVEF: No betablockers versus betablockers.

	Crude OR (95% CI); p value	Adjusted* OR (95% CI); p value with multiple imputation	OR (95% CI); p value with propensity-matching
LVEF ≤ 40% (n=2267)			
In-hospital all-cause mortality	0.76 (0.56-1.03);0.080	0.77 (0.65-0.91); 0.002	0.67 (0.42-1.06);0.088
7-day all-cause mortality	0.73 (0.50-1.08);0.113	0.64 (0.52-0.78);<0.001	0.65 (0.37-1.17);0.149
Need for hospitalisation	0.57 (0.46-0.71);<0.001	0.69 (0.61-0.78);<0.001	0.54 (0.40-0.74);<0.001
Prolonged length of stay (≥ 7 days)	0.78 (0.64-0.95);0.012	0.72 (0.65-0.80);<0.001	0.85 (0.63-1.14);0.271
LVEF 41 – 49% (n=872)			
In-hospital all-cause mortality	0.88 (0.49-1.59);0.682	0.77 (0.56-1.06);0.110	0.73 (0.27-1.98);0.531
7-day all-cause mortality	0.84 (0.40-1.75);0.635	1.13 (0.74-1.72);0.555	0.61 (0.18-2.02);0.409
Need for hospitalisation	0.80 (0.58-1.10);0.172	1.18 (0.98-1.42);0.078	1.00 (0.60-1.68);0.995
Prolonged length of stay (≥ 7 days)	0.97 (0.71-1.32);0.823	0.97 (0.83-1.15);0.749	0.71 (0.44-1.13);0.151
LVEF ≥ 50% (n=6251)			
In-hospital all-cause mortality	0.84 (0.68-1.03);0.086	0.89 (0.88-0.98);0.024	0.88 (0.72-1.07);0.185
7-day all-cause mortality	0.91 (0.70-1.20);0.514	0.87 (0.76-1.00);0.054	0.94 (0.74-1.20);0.609
Need for hospitalisation	0.93 (0.83-1.05);0.232	0.91 (0.86-0.97);0.006	0.96 (0.85-1.07);0.460
Prolonged length of stay (≥ 7 days)	0.88 (0.79-0.99);0.036	0.95 (0.90-1.01);0.082	0.91 (0.81-1.02);0.108

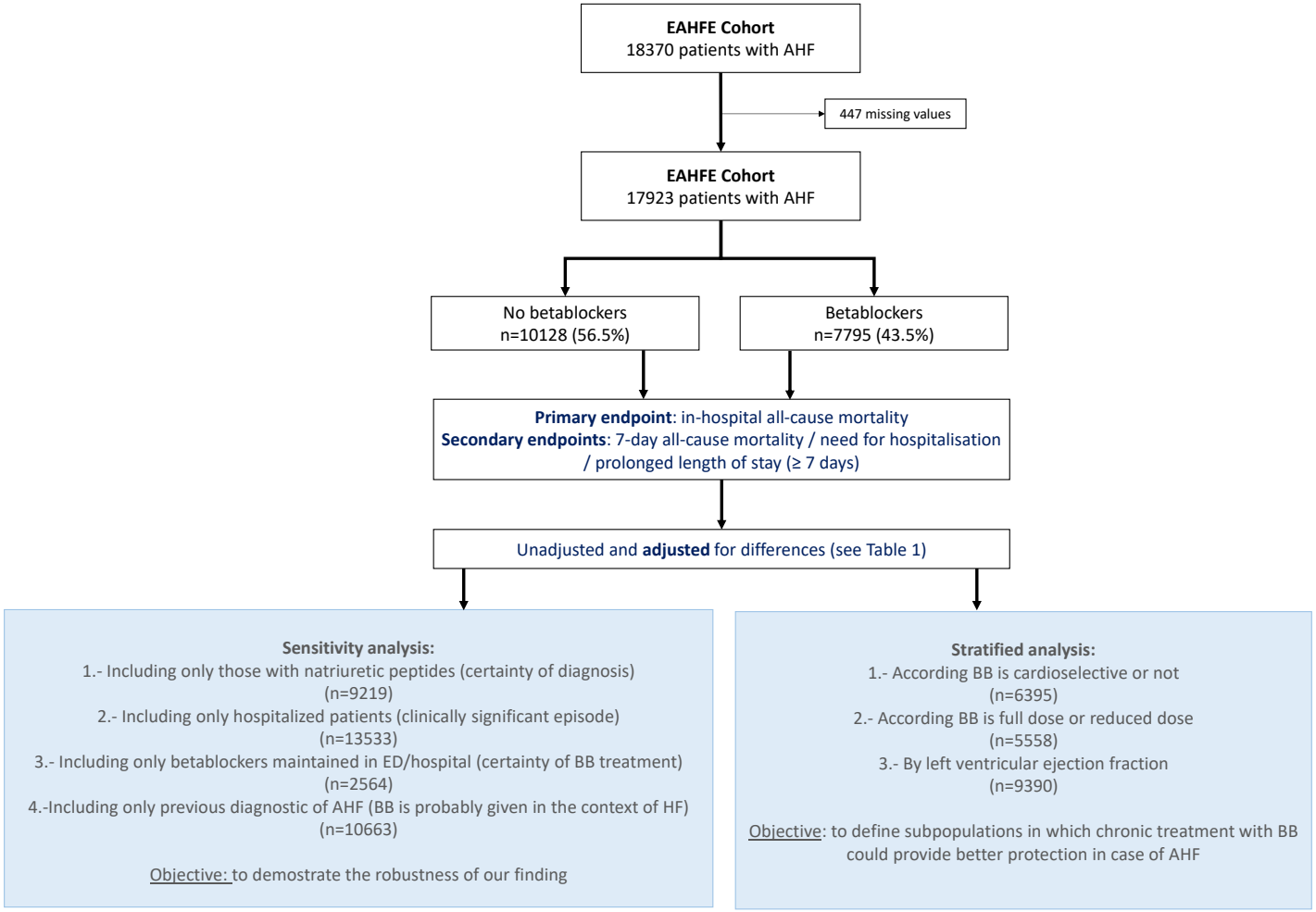
*Adjusted for: age, male sex, arterial hypertension, diabetes mellitus, dyslipaemia, ischaemic heart disease, chronic renal failure, cerebrovascular accident, atrial fibrillation, peripheral artery disease, heart value disease, chronic obstructive pulmonary disease, previous heart failure, Barthel index < 60 points, reduced left ventricle ejection fraction, baseline treatment loop diuretics, angiotensin converter enzyme inhibitors or angiotensin II receptor blocker, mineralocorticoid receptor blocker, calcium channel blockers, digoxin, amiodarone or nitrates; dyspnoea, oedema, symptoms of low cardiac output in acute episode, O2 saturation ≤ 90%, eGFR<60ml/min/1.73m2, NT-proBNP ≥ 5000 pmol/L, use of oxygen therapy or intravenous nitrates in the emergency department.

Supplementary material table 1. Patient characteristics and comparison between groups: included versus not included.

	Total (n=18370)	Included (n=17923)	Not included (n=447)	Missing values	p value
Epidemiologic variables					
Age (years), mean (SD)	80.4 (10.2)	80.4 (10.2)	79.3 (11.2)	29 (0.2)	0.034
Female sex, n (%)	10199 (55.7)	9953 (55.7)	246 (55.4)	46 (0.3)	0.913
Arterial hypertension	15299 (83.5)	14950 (83.6)	349 (80.4)	52 (0.3)	0.078
Diabetes mellitus	7683 (41.9)	7524 (42.1)	159 (36.6)	54 (0.3)	0.023
Dyslipaemia	8030 (43.8)	7881 (44.1)	149 (34.3)	53 (0.3)	<0.001
Ischaemic heart disease	5187 (28.3)	5082 (28.4)	105 (24.2)	54 (0.3)	0.054
Chronic renal failure	4751 (25.9)	4664 (26.1)	87 (20.0)	51 (0.3)	0.005
Cerebrovascular accident	2283 (12.5)	2234 (12.5)	49 (11.3)	53 (0.3)	0.454
Atrial fibrillation	9004 (49.2)	8851 (49.5)	153 (35.3)	53 (0.3)	<0.001
Peripheral artery disease	1653 (9.0)	1626 (9.1)	27 (6.2)	55 (0.3)	0.039
Heart value disease	4692 (25.6)	4566 (25.5)	126 (29.1)	53 (0.3)	0.093
COPD	4286 (23.4)	4181 (23.4)	105 (24.2)	62 (0.3)	0.677
Previous heart failure	10896 (64.0)	10663 (64.1)	233 (58.0)	1339 (7.3)	0.011
Basal status (n, %)					
Barthel index < 60 points	3156 (19.0)	3079 (19.0)	77 (19.2)	8752 (47.6)	0.923
NYHA class III–IV	4311 (24.9)	4211 (24.9)	100 (24.1)	1027 (5.6)	0.717
Reduced LVEF (≤40%)	2311 (24.0)	2267 (24.1)	44 (19.3)	1772 (9.6)	0.091
Baseline treatment (n, %)					
Loop diuretics	11861 (66.2)	11860 (66.2)	1 (14.3)	447 (2.4)	0.007
ACE inhibitors or ARB	10041 (56.0)	10040 (56.0)	1 (25.0)	450 (2.4)	0.326
MRB	2957 (16.5)	2956 (16.5)	1 (25.0)	448 (2.4)	0.514
Calcium channel blockers	4714 (26.3)	4713 (26.3)	1 (25.0)	450 (2.4)	1.000
Digoxin	2671 (14.9)	2670 (14.9)	1 (25.0)	460 (2.5)	0.476
Amiodarone	995 (5.6)	995 (5.6)	0 (0.0)	454 (2.5)	1.000
Nitrates	2978 (16.6)	2978 (16.6)	0 (0.0)	451 (2.5)	1.000
Data of the acute episode (n, %)					
Dyspnoea	16554 (90.4)	16167 (90.5)	387 (88.8)	65 (0.4)	0.229
Oedema	12500 (68.3)	12185 (68.2)	315 (72.2)	61 (0.3)	0.071
Elevated jugular venous pressure	3709 (20.3)	3636 (20.3)	73 (16.7)	64 (0.3)	0.064
Symptoms of low cardiac output [1]	2858 (18.0)	2766 (17.8)	92 (26.1)	2473 (13.5)	<0.001
O2 saturation ≤ 90%	4900 (27.7)	4774 (27.7)	126 (29.6)	708 (3.9)	0.375
SBP ≤ 100 mmHg	1041 (5.8)	1020 (5.8)	21 (4.9)	306 (1.7)	0.435
HR ≤ 100 bpm	12918 (72.5)	12613 (72.5)	305 (71.9)	541 (2.9)	0.808
Hyponatremia [2]	3992 (22.5)	3899 (22.5)	93 (22.0)	649 (3.5)	0.787
eGFR < 60 ml/min/1.73m2	10019 (55.9)	9798 (56.0)	221 (53.1)	446 (2.4)	0.249
NT-proBNP ≥ 5000 pmol/L	3528 (40.2)	3497 (40.2)	31 (39.2)	9587 (52.2)	0.866
Severity of the AHF episode					
MEESSI risk category				8613 (46.9)	0.076
Low risk	3857 (39.5)	3742 (39.4)	115 (45.1)		
Intermediate risk	3910 (40.1)	3810 (40.1)	100 (39.2)		
High risk	1048 (10.7)	1022 (10.8)	26 (10.2)		
Very high risk	942 (9.7)	928 (9.8)	14 (5.5)		
Management in the ED (n, %)					
Use of oxygen therapy	13092 (72.1)	12844 (72.3)	248 (61.7)	215 (1.2)	<0.001
Use of diuretics [3]	15659 (86.2)	15501 (87.3)	158 (39.3)	212 (1.2)	<0.001
Use of endovenous nitrates	2513 (13.8)	2472 (13.9)	41 (10.2)	213 (1.2)	0.033
Use of inotropic or vasopressors	301 (1.7)	289 (1.7)	12 (3.0)	1154 (6.3)	0.056
Use of morphine	944 (6.0)	937 (6.1)	7 (2.1)	2557 (13.9)	0.003
Use of NIV in the ED	1214 (6.7)	1195 (6.7)	19 (4.7)	254 (1.4)	0.109

NYHA: New York Heart Association, COPD: chronic obstructive pulmonary disease, LVEF: left ventricle ejection fraction, ACE: angiotensin converter enzyme, ARB: angiotensin receptor blocker, MRB: mineralocorticoid receptor blocker, SBP: systolic blood pressure, HR: heart rate, bpm: beats per minute, eGFR: estimated glomerular filtration rate, ED: emergency department, NIV: non-invasive ventilation. 1. Symptoms of low cardiac output (cold sweaty extremities, slow capillary refilling, livedo reticularis and/or mental confusion), 2. Hyponatremia (sodium ≤ 135mmol/L), 3. Diuretics in bolus, infusion, or both.

Figure 1. Flow chart for patient inclusion.



AHF: acute heart failure; ED: emergency department; BB: betablockers