Manuscript Number: EJIM-D-19-00204R1

Title: Acute heart failure and adverse events associated with the presence of renal dysfunction and hyperkalaemia. EAHFE- Renal Dysfunction and Hyperkalaemia.

Article Type: Original Article

Keywords: acute heart failure, renal dysfunction, hyperkalaemia, outcomes

Corresponding Author: Dr. Lluís Llauger, MD

Corresponding Author's Institution: Hospital Universitari de Vic

First Author: Javier Jacob, PhD

Order of Authors: Javier Jacob, PhD; Lluís Llauger, MD; Pablo Herrero-Puente, PhD; Francisco-Javier Martín-Sánchez, PhD; Pere Llorens, PhD; Alex Roset, MD; Victor Gil, PhD; Marta Fuentes, MD; Francisco Javier Lucas Imbernón, MD; Òscar Miró, PhD

Abstract: Objective: To study the outcomes of patients with acute heart failure (AHF) presenting renal dysfunction (RD) or hyperkalaemia (Hk) alone or in combination.

Method: We analysed the data of the EAHFE registry, a multicentre, non interventionist cohort with prospective follow-up of patients with AHF. Four groups were defined based on the presence or not of RD or Hk alone or in combination. The primary endpoint was 30-day all-cause mortality.

Results: A total of 11935 of the 13791 patients included in the EAHFE registry were analysed. Of these, 5088 (42.6%) did not have RD or Hk (NoRD-NoHk), 150 (1.3%) had no RD but had Hk (NoRD-Hk), 6012 (50.4%) had RD but not Hk (RD-NoHk) and 685 (5.7%) had both RD and Hk (RD-Hk).

Thirty-day all-cause mortality was greatest in the RD-Hk group with an adjusted Hazard Ratio (HR) of 2.44 (confidence interval 95% [CI95%] 1.67 - 3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (CI95% 1.04 - 1.71; $p = 0.022$). There were no significant differences in in-hospital mortality and reconsultation at 30 days for HF. For the combined endpoint of 30-day all-cause mortality the adjusted HR was 1.33 (CI95% 1.04-1.70); $p = 0.021$) for the RD-Hk group.

Conclusions: The association of 30-day all-cause mortality with the presence of RD and Hk in patients presenting AHF at admission is greater than in those without this combination.

EAHFE- Renal Dysfunction and Hyperkalaemia

Acute heart failure and adverse events associated with the presence of renal
dysfunction and hyperkalaemia.

EAHFE- Renal Dysfunction and Hyperkalaemia

ABSTRACT

Objective: To study the outcomes of patients with acute heart failure (AHF) presenting renal dysfunction (RD) or hyperkalaemia (Hk) alone or in combination.

Method: We analysed the data of the EAHFE registry, a multicentre, non interventionist cohort with prospective follow-up of patients with AHF. Four groups were defined based on the presence or not of RD or Hk alone or in combination. The primary endpoint was 30-day all-cause mortality.

Results: A total of 11935 of the 13791 patients included in the EAHFE registry were analysed. Of these, 5088 (42.6%) did not have RD or Hk (NoRD-NoHk), 150 (1.3%) had no RD but had Hk (NoRD-Hk), 6012 (50.4%) had RD but not Hk (RD-NoHk) and 685 (5.7%) had both RD and Hk (RD-Hk). Thirty-day all-cause mortality was greatest in the RD-Hk group with an adjusted Hazard Ratio (HR) of 2.44 (confidence interval 95% [CI95%] 1.67 – 3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (CI95% 1.04 – 1.71; $p = 0.022$). There were no significant differences in in-hospital mortality and reconsultation at 30 days for HF. For the combined endpoint of 30-day all-cause mortality the adjusted HR was 1.33 (CI95% 1.04-1.70); $p = 0.021$) for the RD-Hk group.

Conclusions: The association of 30-day all-cause mortality with the presence of RD and Hk in patients presenting AHF at admission is greater than in those without this combination.

Key words: acute heart failure, renal dysfunction, hyperkalaemia, outcomes

Introduction

Heart failure (HF) is a syndrome which causes a high mortality and use of health care resources. Acute heart failure (AHF) is one of the main causes of hospitalization in patients with HF and generates the greatest expense among health care costs related to this disease (1). In addition, AHF is associated with bad outcomes with a one-year mortality of 30% (2).

The presence of hyperkalaemia (Hk), defined as a potassium value ≥ 5.5 mEq/L and renal dysfunction (RD) in patients with HF has been related to an increase in adverse events including mortality and the need for hospital admission (3, 4). It has been estimated that the prevalence of Hk and heart failure with reduced ejection fraction (HFrEF) is 3.37% (5). The European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) has reported that the presence of Hk in chronic HF is 2.64%, reaching 4.44% in patients with AHF (6), while in the EAHFE registry (2), the presence of Hk in patients with AHF was 5.6%. The cardiotoxic effects of Hk are severe and may potentially be lethal and difficult to diagnose because of the scarcity of clinical signs and symptoms. In the MEESSI-AHF scale, Hk is a variable associated with a greater risk of 30-day mortality (7). Hk is also related to a greater use of drugs aimed at renin-angiotensin-aldosterone system inhibitors (RAASi), which is one of the therapeutic targets able to reduce the mortality of patients with HFrEF (8).

The prevalence of RD during an episode of AHF is elevated, reaching up to 60% (2), and is related to a worse outcome. Indeed, the higher the estimated glomerular filtration rate (eGFR) the worse the prognosis (3, 6, 9). These results remain the same independently of the formula used to calculate the eGFR, although the Cockcroft-Gault formula, which includes the weight of the patient, seems to be the most accurate (4).

Considering that the presence of RD is related to a greater presence of Hk, it is clear that this combination will have an added effect on the outcome of patients with AHF (10). However, there are few studies on this effect in real life patient cohorts. We hypothesize that the presence of adverse events in patients with both RD and Hk is greater in patients with AHF than the presence of RD or Hk alone.

The aim of this study was to evaluate the outcomes of patients with AHF presenting RD and Hk alone or in combination.

Method

The present study analysed the data of the EAHFE registry (Epidemiology of Acute Heart Failure in Emergency departments), the methodology of which has been described elsewhere (7, 11-13). The EAHFE registry includes a multicentre, multipurpose, non interventionist cohort with prospective follow-up of patients presenting an episode of AHF in the Emergency Department (ED). The inclusion of patients was carried out in 5 phases: EAHFE-1 – from April 15 to May 15, 2007 (1 month, 10 Spanish EDs), EAHFE-2 - from June 1 to 30, 2009 (1 month, 19 EDs), EAHFE-3 – November 1 to December 31, 2011 (2 months, 29 EDs), EAHFE-4 – from February 1 to March 31, 2014 (2 months, 26 EDs) and EAHFE-5 - from January 1 to February 29, 2016 (2 months, 30 EDs). Forty-one Spanish EDs participated in the registry, recruiting a total of 13791 patients. During the inclusion periods case detection was performed by the attending physician using the Framingham criteria (14), and patients provided signed informed consent to participate in the study. Thereafter, the principal investigator of each centre assigned the final diagnosis of each case. The diagnosis was confirmed by determination of natriuretic peptides or the presence of an echocardiogram according to the criteria of the European Society of Cardiology prevailing at the time of the different recruitment periods (8). Patients with an acute coronary syndrome with an elevation of the ST segment were excluded from the study because the outcome depends on the coronary intervention performed. Since this was a non intervention study, the patients received care for the acute episode by the physicians based on internationally accepted protocols and according to the local reference strategies for the management of patients in each participating centre.

A total of 36 independent variables were collected which consisted in: 2 epidemiological variables (age and sex), 8 comorbidities (arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic renal disease, atrial fibrillation, peripheral artery disease, cancer and previous episodes of acute cardiac insufficiency, 3 variables of basal status (Barthel index <60 points, class III - IV of the New York Heart Association [NYHA], Left ventricular ejection fraction <40% [LVEF]), 7 variables of chronic home treatment (loop diuretics, thiazide diuretics, angiotensin converter enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], mineralocorticoid receptor antagonist [MRA], nitrates and oral anticoagulants), 9 variables of the clinical status of the patient at arrival to the ED (dyspnea, orthopnea, oedema, O2 saturation $\leq 90\%$, systolic blood pressure ≤ 100 mmHg, hyponatraemia with sodium values <135 mmol/l, potassium, creatinine and eGFR <60 ml/min/1.73m²), and 7 variables of treatment in the ED (oxygen, intravenous diuretics, intravenous nitrates, inotropic drugs or vasopressors, morphine, non invasive and invasive ventilation).

For this study, only the available values of eGFR and potassium were analyzed at the time of arrival of the patient in the ED. For the comparative study, RD was defined as an eGFR <60ml/min/m² calculated at the time of admission with the MDRD-4 formula (Modification of Diet in Renal Disease), and Hk was defined as potassium levels ≥ 5.5 mmol/L at admission. Patients were classified into four groups based on these two variables: 1) absence of RD and Hk (NoRD-NoHk), 2) absence of RD but presence of Hk (NoRD-Hk), 3) presence of RD but absence of Hk (RD-NoHk), and 4) presence of RD and Hk (RD-Hk).

The principal endpoint of the study was all-cause mortality at 30 days. The secondary endpoints were: in-hospital mortality, reconsultation for AHF within 30 days

after discharge and the combined variable of all-cause mortality or reconsultation for AHF within 30 days. Follow-up was made by a telephone call or by consultation of the hospital and primary care clinical histories of the patients at 30 days after the index episode.

The EAHFE registry was undertaken according to the Declaration of Helsinki of ethical principles for medical investigation in humans, and the patients provided informed consent to participate in the registry. The complete protocol was approved by the Committee of Ethics and Clinical Investigation of the *Hospital Universitario Central of Asturias*, which was the principal committee (protocols 49/2010, 69/2011, 166/13 and 160/15), as well as the committees of the other participating hospitals.

For the statistical analyses, qualitative variables were expressed as absolute values and percentages. Between group differences were analysed using the Chi-squared test (or the Fisher exact test, when appropriate). Quantitative variables were expressed as mean and standard deviation (SD). Differences among groups were determined with the one-way ANOVA test, to determine whether the distribution was normal, the Kolmogorov-Smirnov test was used, and if the distribution did not fulfill normality, the non parametric Kruskal-Wallis test was used. The 30-day all-cause mortality for the 4 groups was evaluated using survival tables and Kaplan-Meier curves and was adjusted by Cox regression with the variables showing significant differences in the univariate study. The reference group was NoRD-NoHk. The results are expressed as hazard ratio (HR) with a confidence interval 95% (CI 95%). In all the cases statistical significance was accepted with a p value less than 0.05 or if the CI95% of the HR excluded the value 1. The statistical analyses were performed using the statistical package SPSS 24.0 (IBM, North Castle, New York, USA).

RESULTS

We analysed the data of 13791 patients. Figure 1 is a flowchart of patient inclusion. Of the 11935 patients finally included in the study, 5088 (42.6%) were in the NoRD-NoHk group, 150 (1.3%) in the NoRD-Hk group, 6012 (50.4%) in the RD-NoHk group and 685 (5.7%) were in the RD-Hk group. The characteristics of the sample and the comparative study among the 4 groups are shown in table 1. Twenty-eight of the 36 variables collected showed significant differences. Table 2 shows the results of the analysis of the crude and adjusted HR for the different groups based on the presence of RD and Hk in the acute episode, with the NoRD-NoHk group being the reference group for all the comparisons. [The values of the beta coefficients for the multivariate analysis are presented in supplementary material, table 1.](#) The principal study variable, 30-day all-cause mortality was greatest in the RD-Hk group with an adjusted HR of 2.44 (CI95% 1.67 – 3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (1.04 – 1.71; $p = 0.022$). The combined variable of 30-day all-cause mortality and reconsultation for AHF was also significantly higher in the RD-Hk group with a HR of 1.33 (CI95% 1.04 – 1.70; $p = 0.021$), but not for the remaining groups. No significant differences were found in the crude or adjusted HR for the remaining variables studied. These results are shown in the survival curve for the principal variable (30-day all-cause death) in the different groups (Figure 2).

[Figure 3 shows the results of the stratified analysis for the primary endpoint, 30-day all-cause death, based on the chronic treatments with ACEI or ARB, MRA, LVEF < 40% or not, and hospital admission or not.](#)

DISCUSSION

The present study shows that the concomitant presence of RD and Hk at admission in patients consulting for AHF is associated with a worse outcome, especially 30-day all-cause mortality.

Patients with AHF have a high prevalence of RD which increases the risk of Hk, especially in those using RAAS inhibitors (15, 16). It is well known that the presence of RD is a predisposing factor for Hk (17). In our study the presence of RD in the whole cohort was 56.1%, with Hk being present in 5.7%. It must be taken into account that the 30-day all-cause mortality in patients with RD and Hk is almost double that of patients with RD without Hk, and this has important implications. Physicians must be especially aware of the characteristics of patients with AHF (18, 19). Patients presenting RD and Hk during an acute episode have the worst prognosis, and therefore, have an elevated profile of risk for adverse events. This is likely because of the greater percentage of hospital admission in this group of greater risk.

The increase in 30-day all-cause mortality in the RD with Hk group is of note taking into account that the Hk without RD group did not present such an unfavorable outcome. On the other hand, the potassium levels in both groups were very similar. It was also of note that this association was not observed in any group in regard to in-hospital all-cause mortality. This was not found in other groups in which the presence of RD with Hk was associated with a worse outcome than Hk without RD (20), suggesting that patients with RD present greater tolerance or adaptation to Hk. One explanation for our results may be related to ED attendance. The ED physicians may have a more tolerant attitude to Hk in patients with RD. They may administer more

1 treatment to reduce the potassium levels in patients not presenting RD, considering
2 that the prognosis of this group is worse because the Hk is acute, while in RD, Hk is
3 chronic and tolerance is greater. Nonetheless, we have no data on the treatment of
4 Hk, and therefore, cannot make any firm conclusions, but the fact that more patients
5 with RD and Hk are admitted than patients without RD but with Hk shows that
6 physicians are more protective of this group.
7
8
9
10
11
12
13
14

15 High potassium levels are related to greater response to diuretics and the
16 presence of RD is related to lower response to diuretics (21, 22). The data of the
17 PROTECT and COACH studies showed an initially linear relationship between potassium
18 levels and death, but this relation was not maintained after multivariate adjustment
19 (23). The authors concluded that the high potassium levels at the time of admission
20 were associated with RD as well as greater response to diuretics, which could explain
21 the lack of association with mortality. It should also be added that loop diuretics
22 produce an elimination of potassium depending on the urine volume. In our study,
23 there were no differences in the use of intravenous loop diuretics in the ED, but the
24 dose of the diuretic or the volume of diuresis were not collected, and therefore, we
25 cannot conclude that the response to diuretics influenced our results.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42

43 Our results show that the initiation of treatment with potassium binders should
44 be evaluated in patients with AHF and the presence of Hk, especially if RD is also
45 present. The new binders agents currently available are better tolerated and have
46 demonstrated to be effective in reducing potassium levels (24 - 26), although it has not
47 been demonstrated that they reduce the mortality of these patients (27). Neither is
48 there evidence of the benefits of emergency treatment of Hk (28) on patient outcome.
49 Since we did not find any association with in-hospital all-cause mortality in any group,
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

we believe that it is especially important to treat Hk with binders at hospital discharge following hospitalization or ED care.

Special attention is required by patients receiving RAASi. In the analysis by subgroups we found that, in patients with RD (either with or without concurrent Hk), the use of ACEI or ARB would avoid increases in 30-day mortality with respect to patients without RD and Hk (control group), a situation that it is not observed for patients not taking ACEI or ARB. Conversely, in patients with RD and Hk, the use of MRA is associated with a higher increase in 30-day mortality compared to control group patients than patients not taking MRA. Physicians should be especially sensitive to the MRA in the presence of RD and Hk.

Our study has several limitations. The most important being that it involved a registry of a prospective cohort, and therefore, conclusions are made on associations among variables. As mentioned previously, two variables which may influence the results of patient outcomes were not collected and these were the treatment of Hk and diuretic treatment and response to this treatment. However, the study has the strength of being a real life cohort with which points of improvement in daily clinical practice can be identified. Other limitation of the present analysis is the lack of adjustment for important potential confounders such as discharge treatment and doses.

In conclusion, the results of this study have important clinical applications. Taking into account the association between RD with Hk and mortality, clinicians must be especially aware of the presence of Hk in patients with RD. In this respect, potassium binders may improve the outcomes of these patients. Nonetheless, clinical studies are needed to study prognostic variables in patients with AHF.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

REFERENCES

1. Delgado JF, Oliva J, Llano M, Pascual-Figal D, Grillo JJ, Comín-Colet J et al. Health care and nonhealth care costs in the treatment of patients with symptomatic chronic heart failure in Spain. *Rev Esp Cardiol.* 2014;67:643-50.
2. Llorens P, Javaloyes P, Martín-Sánchez FJ, Jacob J, Herrero-Puente P, Gil V et al. Time trends in characteristics, clinical course, and outcomes of 13,791 patients with acute heart failure. *Clin Res Cardiol.* 2018;107:897-913.
3. Cioffi G, Mortara A, Di Lenarda A, Oliva F, Lucci D, Senni M, et al. Clinical features, and in-hospital and 1-year mortalities of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Int J Cardiol.* 2013;168:3691–7.39.
4. Weidmann ZM, Breidthardt T, Twerenbold R, Zuesli C, Nowak A, von Eckardstein A, et al. Prediction of mortality using quantification of renal function in acute heart failure. *Int J Cardiol.* 2015;201:650–7.
5. Hernández Á, Delgado JF, Cinca J, Fernández-Avilés F, Marrugat J. Prevalence and incidence of hyperkalaemia in the Spanish population with heart failure with reduced ejection fraction: a systematic review and populational relevance. *Rev Clin Esp.* 2018;218:253-60.
6. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail.* 2016;18:613-25.

- 1 7. Miró Ò, Rossello X, Gil V, Martín-Sánchez FJ, Llorens P, Herrero-Puente P et al.
2 Predicting 30-Day Mortality for Patients With Acute Heart Failure in the
3 Emergency Department: A Cohort Study. *Ann Intern Med.* 2017;167:698-705.
4
5
6
7
- 8 8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016
9 ESC Guidelines for the diagnosis and treatment of acute and chronic heart
10 failure: The Task Force for the diagnosis and treatment of acute and chronic
11 heart failure of the European Society of Cardiology (ESC) Developed with the
12 special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart*
13 *J.* 2016;18:891-975.
14
15
16
17
18
19
20
21
22
23
24
- 25 9. Llauger L, Jacob J, Miró Ò. Renal function and acute heart failure outcome. *Med*
26 *Clin (Barc).* 2018;151:281-90.
27
28
29
30
- 31 10. Jain N, Kotla S, Little BB, Weideman RA, Brilakis ES, Reilly RF et al. Predictors of
32 hyperkalemia and death in patients with cardiac and renal disease. *Am J*
33 *Cardiol.* 2012;109:1510-3.
34
35
36
37
38
39
- 40 11. Llorens P, Escoda R, Miró O, Herrero Puente P, Martín-Sánchez FJ, Jacob J, et al.
41 Characteristics and clinical course of patients with acute heart failure and the
42 therapeutic measures applied in Spanish emergency departments: based on
43 the EAHFE registry (Epidemiology of acute heart failure in Emergency
44 Departments). *Emergencias.* 2015;27:11-22.
45
46
47
48
49
50
51
52
- 53 12. Miró O, Llorens P, Escalada X, Herrero P, Jacob J, Gil V, et al. Prehospital
54 emergency care of patients with acute heart failure in Spain: the SEMICA study
55
56
57
58
59
60
61
62
63
64
65

(Emergency Medical Response Systems for Patients with acute heart failure).

Emergencias. 2017;29:223-30.

13. Llauger L, Jacob J, Corominas Lasalle G, Puig Martorell J, González Casquet P, Bullon Chia A. Renal insufficiency and hyperkalemia in acute heart failure. Emergencias. 2018;30:357-8.

14. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88:107-15.

15. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351:543-51.

16. Adams KF Jr., Fonarow GC, Emerman CL, et al., ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209–16.

17. Michel A, Martín-Pérez M, Ruigómez A, García Rodríguez LA. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. Eur J Heart Fail. 2015;17:205-13.

18. Llorens P. Risk assessment in emergency department patients with acute heart failure: We need to reach beyond our clinical judgment. *Emergencias*. 2018;30:75-6.
19. Formiga F, Chivite D. Acute heart failure: Understanding the patient is essential. *Emergencias*. 2018;30:145-6.
20. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;169:1156 –1162.
21. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome-an analysis from RELAX-AHF. *Eur J Heart Fail* 2014;16:1230e1240.
22. ter Maaten JM, Valente MA, Metra M, Bruno N, O'Connor CM, Ponikowski P, et al. A combined clinical and biomarker approach to predict diuretic response in acute heart failure. *Clin Res Cardiol* 2016;105:145-53.
23. Tromp J, Ter Maaten JM, Damman K, O'Connor CM, Metra M, Dittrich HC et al. Serum Potassium Levels and Outcome in Acute Heart Failure (Data from the PROTECT and COACH Trials). *Am J Cardiol*. 2017;119:290-96.
24. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372:211-21.

25. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, et al.
Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder,
in a double-blind, placebo-controlled study in patients with chronic heart
failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32:820 – 25.
26. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G,
Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. *N
Engl J Med*. 2015;372:222–31.
27. Das S, Dey JK, Sen S, Mukherjee R. Efficacy and Safety of Patiromer in
Hyperkalemia: A Systematic Review and Meta-Analysis. *J Pharm Pract*.
2018;31:6-17.
28. Mahoney BA, Smith WA, Lo D, Tsoi K, Tonelli M, Clase C. Emergency
interventions for hyperkalaemia. *Cochrane Database Syst Rev*.
2005;2:CD003235.

Figure 1. Flowchart of patient inclusion in the present study. EAHFE: Epidemiology of Acute Heart Failure in Emergency departments.

Table 1. Characteristics of the global cohort and the four groups classified according to the presence or not of renal dysfunction (RD) and hyperkalaemia (Hk).

	Total (n=11935)	NoRD-NoHk (n=5088)	NoRD-Hk (n=150)	RD-NoHk (n=6012)	RD-Hk (n=685)	P value
Demographic data (n, %)						
Age (years) [†]	80.1 ± 10.1	78.0 ± 11.1	77.2 ± 11.1	81.8 ± 9.0	81.4 ± 9.6	< 0.001
Age ≥ 75 years	9040 (75.7)	3512 (69.0)	98 (65.3)	4880 (81.2)	550 (80.3)	< 0.001
Male	5324 (44.6)	2565 (50.4)	79 (52.7)	2394 (39.8)	286 (41.8)	< 0.001
Personal history (n, %)						
Arterial hypertension	10001 (84.0)	4015 (79.1)	119 (79.9)	5279 (88.0)	588 (86.0)	< 0.001
Diabetes mellitus	5053 (42.4)	1879 (37.2)	78 (52.3)	2712 (45.2)	384 (56.1)	< 0.001
Ischaemic heart disease	3452 (29.0)	1276 (25.1)	41 (27.5)	1940 (32.3)	195 (28.5)	< 0.001
Chronic kidney failure	3117 (26.2)	279 (5.5)	17 (11.4)	2494 (41.5)	327 (47.8)	< 0.001
Atrial fibrillation	5847 (49.1)	2421 (47.7)	76 (51.0)	3039 (50.6)	311 (45.5)	0.004
Peripheral artery disease	1089 (9.1)	366 (7.2)	16 (10.7)	626 (10.4)	81 (11.8)	< 0.001
Cancer	1508 (14.3)	640 (14.1)	22 (16.3)	762 (14.5)	84 (13.9)	0.844
Prior episode of heart failure	6979 (59.5)	2616 (52.4)	83 (56.8)	3848 (65.1)	432 (63.8)	< 0.001
Basal situation (n, %)						
Barthel Index < 60 points	1907 (18.2)	638 (14.4)	23 (17.8)	1100 (20.6)	146 (25.3)	< 0.001
NYHA functional class III–IV	2736 (24.5)	949 (20.0)	38 (27.7)	1554 (27.6)	195 (31.2)	< 0.001
LVEF < 40%	1397 (21.8)	518 (19.9)	23 (28.8)	762 (22.5)	94 (27.9)	0.001
Chronic treatments (n, %)						
Loop diuretics	7685 (66.5)	2872 (58.5)	83 (56.5)	4268 (73.3)	462 (69.0)	< 0.001
Thiazide diuretics	1687 (14.6)	727 (14.8)	14 (9.5)	856 (14.7)	90 (13.4)	0.264
ACEI or ARB	6638 (57.5)	2839 (57.8)	95 (64.6)	3293 (56.5)	411 (61.3)	0.023
MRA	1974 (17.1)	731 (14.9)	31 (21.1)	1048 (18.0)	164 (24.5)	< 0.001
Beta-blocker	4806 (41.6)	1899 (38.7)	68 (46.3)	2554 (43.9)	285 (42.5)	< 0.001
Nitrates	2073 (17.9)	677 (13.8)	26 (17.7)	1244 (21.4)	126 (18.8)	< 0.001
Oral anticoagulation	2168 (18.8)	920 (18.7)	34 (23.1)	1099 (18.9)	115 (17.2)	0.391
Data of the acute episode (n, %)						
Dyspnea	10824 (91.0)	4635 (91.4)	132 (89.2)	5452 (91.0)	605 (88.8)	0.135
Orthopnoea	6617 (55.7)	2781 (54.9)	79 (53.4)	3361 (56.1)	396 (58.2)	0.271
Oedema	8068 (67.8)	3328 (65.6)	99 (66.9)	4162 (69.5)	479 (70.3)	< 0.001
O ₂ saturation ≤ 90%	3233 (28.1)	1312 (26.7)	47 (32.9)	1631 (28.1)	243 (37.1)	< 0.001
SBP ≤ 100 mmHg	650 (5.5)	180 (3.6)	12 (8.2)	382 (6.4)	76 (11.4)	< 0.001
Hyponatremia (<135 mmol/l)	2175 (18.3)	860 (17.0)	55 (36.7)	1019 (17.1)	241 (35.5)	< 0.001
Potassium (mmol/L) [†]	4.42 ± 0.69	4.19 ± 0.51	6.04 ± 0.86	4.39 ± 0.54	6.00 ± 0.60	< 0.001
Creatinine (mg/dl) [†]	1.36 ± 0.85	0.85 ± 0.19	0.90 ± 0.18	1.70 ± 0.90	2.19 ± 1.21	< 0.001
eGFR (ml/min/m ²) [†]	59.10 ± 27.65	84.15 ± 20.71	79.05 ± 17.89	40.45 ± 12.54	32.34 ± 13.10	< 0.001
Treatment in ED (n, %)						
Need for oxygen	8631 (73.1)	3650 (72.5)	105 (70.0)	4379 (73.6)	497 (73.5)	0.450
Need for intravenous diuretics ‡	10214 (86.7)	4326 (86.1)	131 (87.3)	5163 (87.0)	594 (88.0)	0.345
Need for intravenous nitrates	1815 (15.4)	754 (15.0)	29 (19.3)	932 (15.7)	100 (14.8)	0.390
Need for inotropic or vasopressor	237 (2.0)	53 (1.1)	7 (4.7)	128 (2.2)	49 (7.3)	< 0.001
Need for morphine	644 (6.1)	238 (5.3)	11 (8.1)	333 (6.4)	62 (10.3)	< 0.001
Need for non-invasive ventilation	821 (7.0)	271 (5.4)	14 (9.3)	430 (7.2)	106 (15.7)	< 0.001
Need for invasive ventilation	315 (2.7)	138 (2.7)	3 (2.0)	157 (2.6)	17 (2.5)	0.930
Evolutive data (n, %)						
Hospital admission	9013 (75.6)	3647 (71.7)	118 (78.7)	4653 (77.5)	595 (86.9)	< 0.001
Stay (days) [†]	7.7 ± 12.3	6.9 ± 10.4	9.9 ± 25.5	8.1 ± 12.4	9.6 ± 18.1	< 0.001

[†]Values are mean ± SD, n (%). RD: renal dysfunction. Hk Hyperkalaemia. Chronic kidney failure (creatinine > 2mg/dl), NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. SBP: Systolic blood pressure. ED: emergency department. eGFR: estimated glomerular filtration rate, calculated with the formula MDRD-4 (Modification of Diet in Renal Disease). ‡ Use of loop diuretics in perfusion, in bolus or both.

Table 2. Crude and adjusted Hazard Ratios (HR) for the different groups based on the presence of renal dysfunction (RD) and hyperkalaemia (Hk) during the episode of acute heart failure.

	Crude HR (CI 95%)	P value	Adjusted HR (CI 95%)	P value
Primary endpoint				
30-day all-cause mortality				
NoRD-NoHk	reference		reference	
NoRD-Hk	2.06 (1.31 – 3.23)	0.002	1.17 (0.51 – 2.69)	0.714
RD-NoHk	1.64 (1.44 – 1.87)	< 0.001	1.34 (1.04 – 1.71)	0.022
RD-Hk	4.23 (3.52 – 5.07)	< 0.001	2.44 (1.67 – 3.55)	< 0.001
Secondary endpoint				
In-hospital all-cause mortality				
NoRD-NoHk	reference		reference	
NoRD-Hk	1.21 (0.74 – 1.97)	0.455	0.98 (0.40 – 2.40)	0.996
RD-NoHk	1.04 (0.89 – 1.21)	0.641	0.95 (0.70 – 1.29)	0.747
RD-Hk	1.31 (1.07 – 1.62)	0.010	0.95 (0.61 – 1.49)	0.831
30-day ED reconsultation for HF				
NoRD-NoHk	reference	-	reference	
NoRD-Hk	1.22 (0.85 – 1.75)	0.275	0.86 (0.47 – 1.57)	0.621
RD-NoHk	1.27 (1.17 – 1.38)	< 0.001	1.06 (0.92 – 1.23)	0.422
RD-Hk	1.35 (1.13 – 1.61)	0.001	1.06 (0.78 – 1.45)	0.703
30-day all-cause death or ED reconsultation for HF				
NoRD-NoHk	reference	-	reference	
NoRD-Hk	1.43 (1.08 – 1.91)	0.014	1.00 (0.62 – 1.63)	0.996
RD-NoHk	1.34 (1.25 – 1.44)	< 0.001	1.08 (0.95 – 1.23)	0.223
RD-Hk	2.01 (1.78 – 2.29)	< 0.001	1.33 (1.04 – 1.70)	0.021

Adjusted: male, age ≥ 75 years, personal history of arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic kidney failure, atrial fibrillation, peripheral artery disease or prior episode of heart failure; basal situation with Barthel Index < 60 points, NYHA functional class III–IV or left ventricular ejection fraction $< 40\%$; chronic treatments with loop diuretics, angiotensin-converter enzyme inhibitor or angiotensin receptor blocker, mineralocorticoid receptor antagonist, beta-blocker or nitrates; acute episode with oedema, O₂ saturation $\leq 90\%$, systolic blood pressure ≤ 100 mmHg or hyponatremia (sodium < 135 mmol/l); need in emergency department of inotropic or vasopressor, morphine or non-invasive ventilation, and hospital admission.

Figure 2. Survival curve adjusted for the primary endpoint (30-day all-cause mortality) in the different study groups.

Figure 3. Stratified analysis of the adjusted hazard ratios (HR) for primary endpoint (30-day all-cause mortality) the different groups based on the presence of renal dysfunction (RD), hyperkalaemia (Hk) or both during the episode of acute heart failure (reference group NoRD-NoHk).

RD: renal dysfunction. Hk Hyperkalaemia. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. nc: not calculated, because the sample size does not allow it.

EAHFE- Renal Dysfunction and Hyperkalaemia

Acute heart failure and adverse events associated with the presence of renal dysfunction and hyperkalaemia.

EAHFE- Renal Dysfunction and Hyperkalaemia

ABSTRACT

Objective: To study the outcomes of patients with acute heart failure (AHF) presenting renal dysfunction (RD) or hyperkalaemia (Hk) alone or in combination.

Method: We analysed the data of the EAHFE registry, a multicentre, non interventionist cohort with prospective follow-up of patients with AHF. Four groups were defined based on the presence or not of RD or Hk alone or in combination. The primary endpoint was 30-day all-cause mortality.

Results: A total of 11935 of the 13791 patients included in the EAHFE registry were analysed. Of these, 5088 (42.6%) did not have RD or Hk (NoRD-NoHk), 150 (1.3%) had no RD but had Hk (NoRD-Hk), 6012 (50.4%) had RD but not Hk (RD-NoHk) and 685 (5.7%) had both RD and Hk (RD-Hk). Thirty-day all-cause mortality was greatest in the RD-Hk group with an adjusted Hazard Ratio (HR) of 2.44 (confidence interval 95% [CI95%] 1.67 – 3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (CI95% 1.04 – 1.71; $p = 0.022$). There were no significant differences in in-hospital mortality and reconsultation at 30 days for HF. For the combined endpoint of 30-day all-cause mortality the adjusted HR was 1.33 (CI95% 1.04-1.70); $p = 0.021$) for the RD-Hk group.

Conclusions: The association of 30-day all-cause mortality with the presence of RD and Hk in patients presenting AHF at admission is greater than in those without this combination.

Key words: acute heart failure, renal dysfunction, hyperkalaemia, outcomes

Introduction

Heart failure (HF) is a syndrome which causes a high mortality and use of health care resources. Acute heart failure (AHF) is one of the main causes of hospitalization in patients with HF and generates the greatest expense among health care costs related to this disease (1). In addition, AHF is associated with bad outcomes with a one-year mortality of 30% (2).

The presence of hyperkalaemia (Hk), defined as a potassium value ≥ 5.5 mEq/L and renal dysfunction (RD) in patients with HF has been related to an increase in adverse events including mortality and the need for hospital admission (3, 4). It has been estimated that the prevalence of Hk and heart failure with reduced ejection fraction (HFrEF) is 3.37% (5). The European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) has reported that the presence of Hk in chronic HF is 2.64%, reaching 4.44% in patients with AHF (6), while in the EAHFE registry (2), the presence of Hk in patients with AHF was 5.6%. The cardiotoxic effects of Hk are severe and may potentially be lethal and difficult to diagnose because of the scarcity of clinical signs and symptoms. In the MEESSI-AHF scale, Hk is a variable associated with a greater risk of 30-day mortality (7). Hk is also related to a greater use of drugs aimed at renin-angiotensin-aldosterone system inhibitors (RAASi), which is one of the therapeutic targets able to reduce the mortality of patients with HFrEF (8).

The prevalence of RD during an episode of AHF is elevated, reaching up to 60% (2), and is related to a worse outcome. Indeed, the higher the estimated glomerular filtration rate (eGFR) the worse the prognosis (3, 6, 9). These results remain the same independently of the formula used to calculate the eGFR, although the Cockcroft-Gault formula, which includes the weight of the patient, seems to be the most accurate (4).

Considering that the presence of RD is related to a greater presence of Hk, it is clear that this combination will have an added effect on the outcome of patients with AHF (10). However, there are few studies on this effect in real life patient cohorts. We hypothesize that the presence of adverse events in patients with both RD and Hk is greater in patients with AHF than the presence of RD or Hk alone.

The aim of this study was to evaluate the outcomes of patients with AHF presenting RD and Hk alone or in combination.

Method

The present study analysed the data of the EAHFE registry (Epidemiology of Acute Heart Failure in Emergency departments), the methodology of which has been described elsewhere (7, 11-13). The EAHFE registry includes a multicentre, multipurpose, non interventionist cohort with prospective follow-up of patients presenting an episode of AHF in the Emergency Department (ED). The inclusion of patients was carried out in 5 phases: EAHFE-1 – from April 15 to May 15, 2007 (1 month, 10 Spanish EDs), EAHFE-2 - from June 1 to 30, 2009 (1 month, 19 EDs), EAHFE-3 – November 1 to December 31, 2011 (2 months, 29 EDs), EAHFE-4 – from February 1 to March 31, 2014 (2 months, 26 EDs) and EAHFE-5 - from January 1 to February 29, 2016 (2 months, 30 EDs). Forty-one Spanish EDs participated in the registry, recruiting a total of 13791 patients. During the inclusion periods case detection was performed by the attending physician using the Framingham criteria (14), and patients provided signed informed consent to participate in the study. Thereafter, the principal investigator of each centre assigned the final diagnosis of each case. The diagnosis was confirmed by determination of natriuretic peptides or the presence of an echocardiogram according to the criteria of the European Society of Cardiology prevailing at the time of the different recruitment periods (8). Patients with an acute coronary syndrome with an elevation of the ST segment were excluded from the study because the outcome depends on the coronary intervention performed. Since this was a non intervention study, the patients received care for the acute episode by the physicians based on internationally accepted protocols and according to the local reference strategies for the management of patients in each participating centre.

A total of 36 independent variables were collected which consisted in: 2 epidemiological variables (age and sex), 8 comorbidities (arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic renal disease, atrial fibrillation, peripheral artery disease, cancer and previous episodes of acute cardiac insufficiency, 3 variables of basal status (Barthel index <60 points, class III - IV of the New York Heart Association [NYHA], Left ventricular ejection fraction <40% [LVEF]), 7 variables of chronic home treatment (loop diuretics, thiazide diuretics, angiotensin converter enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], mineralocorticoid receptor antagonist [MRA], nitrates and oral anticoagulants), 9 variables of the clinical status of the patient at arrival to the ED (dyspnea, orthopnea, oedema, O₂ saturation $\leq$ 90%, systolic blood pressure $\leq$ 100 mmHg, hyponatraemia with sodium values <135 mmol/l, potassium, creatinine and eGFR <60 ml/min/1.73m²), and 7 variables of treatment in the ED (oxygen, intravenous diuretics, intravenous nitrates, inotropic drugs or vasopressors, morphine, non invasive and invasive ventilation).

For this study, only the available values of eGFR and potassium were analyzed at the time of arrival of the patient in the ED. For the comparative study, RD was defined as an eGFR <60ml/min/m² calculated at the time of admission with the MDRD-4 formula (Modification of Diet in Renal Disease), and Hk was defined as potassium levels $\geq$ 5.5mmol/L at admission. Patients were classified into four groups based on these two variables: 1) absence of RD and Hk (NoRD-NoHk), 2) absence of RD but presence of Hk (NoRD-Hk), 3) presence of RD but absence of Hk (RD-NoHk), and 4) presence of RD and Hk (RD-Hk).

The principal endpoint of the study was all-cause mortality at 30 days. The secondary endpoints were: in-hospital mortality, reconsultation for AHF within 30 days

after discharge and the combined variable of all-cause mortality or reconsultation for AHF within 30 days. Follow-up was made by a telephone call or by consultation of the hospital and primary care clinical histories of the patients at 30 days after the index episode.

The EAHFE registry was undertaken according to the Declaration of Helsinki of ethical principles for medical investigation in humans, and the patients provided informed consent to participate in the registry. The complete protocol was approved by the Committee of Ethics and Clinical Investigation of the *Hospital Universitario Central of Asturias*, which was the principal committee (protocols 49/2010, 69/2011, 166/13 and 160/15), as well as the committees of the other participating hospitals.

For the statistical analyses, qualitative variables were expressed as absolute values and percentages. Between group differences were analysed using the Chi-squared test (or the Fisher exact test, when appropriate). Quantitative variables were expressed as mean and standard deviation (SD). Differences among groups were determined with the one-way ANOVA test, to determine whether the distribution was normal, the Kolmogorov-Smirnov test was used, and if the distribution did not fulfill normality, the non parametric Kruskal-Wallis test was used. The 30-day all-cause mortality for the 4 groups was evaluated using survival tables and Kaplan-Meier curves and was adjusted by Cox regression with the variables showing significant differences in the univariate study. The reference group was NoRD-NoHk. The results are expressed as hazard ratio (HR) with a confidence interval 95% (CI 95%). In all the cases statistical significance was accepted with a p value less than 0.05 or if the CI95% of the HR excluded the value 1. The statistical analyses were performed using the statistical package SPSS 24.0 (IBM, North Castle, New York, USA).

RESULTS

We analysed the data of 13791 patients. Figure 1 is a flowchart of patient inclusion. Of the 11935 patients finally included in the study, 5088 (42.6%) were in the NoRD-NoHk group, 150 (1.3%) in the NoRD-Hk group, 6012 (50.4%) in the RD-NoHk group and 685 (5.7%) were in the RD-Hk group. The characteristics of the sample and the comparative study among the 4 groups are shown in table 1. Twenty-eight of the 36 variables collected showed significant differences. Table 2 shows the results of the analysis of the crude and adjusted HR for the different groups based on the presence of RD and Hk in the acute episode, with the NoRD-NoHk group being the reference group for all the comparisons. [The values of the beta coefficients for the multivariate analysis are presented in supplementary material, table 1.](#) The principal study variable, 30-day all-cause mortality was greatest in the RD-Hk group with an adjusted HR of 2.44 (CI95% 1.67 – 3.55; $p < 0.001$) and in the RD-NoHk group with an adjusted HR of 1.34 (1.04 – 1.71; $p = 0.022$). The combined variable of 30-day all-cause mortality and reconsultation for AHF was also significantly higher in the RD-Hk group with a HR of 1.33 (CI95% 1.04 – 1.70; $p = 0.021$), but not for the remaining groups. No significant differences were found in the crude or adjusted HR for the remaining variables studied. These results are shown in the survival curve for the principal variable (30-day all-cause death) in the different groups (Figure 2).

[Figure 3 shows the results of the stratified analysis for the primary endpoint, 30-day all-cause death, based on the chronic treatments with ACEI or ARB, MRA, LVEF < 40% or not, and hospital admission or not.](#)

DISCUSSION

The present study shows that the concomitant presence of RD and Hk at admission in patients consulting for AHF is associated with a worse outcome, especially 30-day all-cause mortality.

Patients with AHF have a high prevalence of RD which increases the risk of Hk, especially in those using RAAS inhibitors (15, 16). It is well known that the presence of RD is a predisposing factor for Hk (17). In our study the presence of RD in the whole cohort was 56.1%, with Hk being present in 5.7%. It must be taken into account that the 30-day all-cause mortality in patients with RD and Hk is almost double that of patients with RD without Hk, and this has important implications. Physicians must be especially aware of the characteristics of patients with AHF (18, 19). Patients presenting RD and Hk during an acute episode have the worst prognosis, and therefore, have an elevated profile of risk for adverse events. This is likely because of the greater percentage of hospital admission in this group of greater risk.

The increase in 30-day all-cause mortality in the RD with Hk group is of note taking into account that the Hk without RD group did not present such an unfavorable outcome. On the other hand, the potassium levels in both groups were very similar. It was also of note that this association was not observed in any group in regard to in-hospital all-cause mortality. This was not found in other groups in which the presence of RD with Hk was associated with a worse outcome than Hk without RD (20), suggesting that patients with RD present greater tolerance or adaptation to Hk. One explanation for our results may be related to ED attendance. The ED physicians may have a more tolerant attitude to Hk in patients with RD. They may administer more

treatment to reduce the potassium levels in patients not presenting RD, considering that the prognosis of this group is worse because the Hk is acute, while in RD, Hk is chronic and tolerance is greater. Nonetheless, we have no data on the treatment of Hk, and therefore, cannot make any firm conclusions, but the fact that more patients with RD and Hk are admitted than patients without RD but with Hk shows that physicians are more protective of this group.

High potassium levels are related to greater response to diuretics and the presence of RD is related to lower response to diuretics (21, 22). The data of the PROTECT and COACH studies showed an initially linear relationship between potassium levels and death, but this relation was not maintained after multivariate adjustment (23). The authors concluded that the high potassium levels at the time of admission were associated with RD as well as greater response to diuretics, which could explain the lack of association with mortality. It should also be added that loop diuretics produce an elimination of potassium depending on the urine volume. In our study, there were no differences in the use of intravenous loop diuretics in the ED, but the dose of the diuretic or the volume of diuresis were not collected, and therefore, we cannot conclude that the response to diuretics influenced our results.

Our results show that the initiation of treatment with potassium binders should be evaluated in patients with AHF and the presence of Hk, especially if RD is also present. The new binders agents currently available are better tolerated and have demonstrated to be effective in reducing potassium levels (24 - 26), although it has not been demonstrated that they reduce the mortality of these patients (27). Neither is there evidence of the benefits of emergency treatment of Hk (28) on patient outcome. Since we did not find any association with in-hospital all-cause mortality in any group,

we believe that it is especially important to treat Hk with binders at hospital discharge following hospitalization or ED care.

Special attention is required by patients receiving RAASi. In the analysis by subgroups we found that, in patients with RD (either with or without concurrent Hk), the use of ACEI or ARB would avoid increases in 30-day mortality with respect to patients without RD and Hk (control group), a situation that it is not observed for patients not taking ACEI or ARB. Conversely, in patients with RD and Hk, the use of MRA is associated with a higher increase in 30-day mortality compared to control group patients than patients not taking MRA. Physicians should be especially sensitive to the MRA in the presence of RD and Hk.

Our study has several limitations. The most important being that it involved a registry of a prospective cohort, and therefore, conclusions are made on associations among variables. As mentioned previously, two variables which may influence the results of patient outcomes were not collected and these were the treatment of Hk and diuretic treatment and response to this treatment. However, the study has the strength of being a real life cohort with which points of improvement in daily clinical practice can be identified. Other limitation of the present analysis is the lack of adjustment for important potential confounders such as discharge treatment and doses.

In conclusion, the results of this study have important clinical applications. Taking into account the association between RD with Hk and mortality, clinicians must be especially aware of the presence of Hk in patients with RD. In this respect, potassium binders may improve the outcomes of these patients. Nonetheless, clinical studies are needed to study prognostic variables in patients with AHF.

REFERENCES

1. Delgado JF, Oliva J, Llano M, Pascual-Figal D, Grillo JJ, Comín-Colet J et al. Health care and nonhealth care costs in the treatment of patients with symptomatic chronic heart failure in Spain. *Rev Esp Cardiol*. 2014;67:643-50.
2. Llorens P, Javaloyes P, Martín-Sánchez FJ, Jacob J, Herrero-Puente P, Gil V et al. Time trends in characteristics, clinical course, and outcomes of 13,791 patients with acute heart failure. *Clin Res Cardiol*. 2018;107:897-913.
3. Cioffi G, Mortara A, Di Lenarda A, Oliva F, Lucci D, Senni M, et al. Clinical features, and in-hospital and 1-year mortalities of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Int J Cardiol*. 2013;168:3691–7.39.
4. Weidmann ZM, Breidthardt T, Twerenbold R, Zuesli C, Nowak A, von Eckardstein A, et al. Prediction of mortality using quantification of renal function in acute heart failure. *Int J Cardiol*. 2015;201:650–7.
5. Hernández Á, Delgado JF, Cinca J, Fernández-Avilés F, Marrugat J. Prevalence and incidence of hyperkalaemia in the Spanish population with heart failure with reduced ejection fraction: a systematic review and populational relevance. *Rev Clin Esp*. 2018;218:253-60.
6. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18:613-25.

7. Miró Ò, Rossello X, Gil V, Martín-Sánchez FJ, Llorens P, Herrero-Puente P et al. Predicting 30-Day Mortality for Patients With Acute Heart Failure in the Emergency Department: A Cohort Study. *Ann Intern Med.* 2017;167:698-705.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;18:891-975.
9. Llauger L, Jacob J, Miró Ò. Renal function and acute heart failure outcome. *Med Clin (Barc).* 2018;151:281-90.
10. Jain N, Kotla S, Little BB, Weideman RA, Brilakis ES, Reilly RF et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol.* 2012;109:1510-3.
11. Llorens P, Escoda R, Miró O, Herrero Puente P, Martín-Sánchez FJ, Jacob J, et al. Characteristics and clinical course of patients with acute heart failure and the therapeutic measures applied in Spanish emergency departments: based on the EAHFE registry (Epidemiology of acute heart failure in Emergency Departments). *Emergencias.* 2015;27:11-22.
12. Miró O, Llorens P, Escalada X, Herrero P, Jacob J, Gil V, et al. Prehospital emergency care of patients with acute heart failure in Spain: the SEMICA study

(Emergency Medical Response Systems for Patients with acute heart failure).

Emergencias. 2017;29:223-30.

13. Llauger L, Jacob J, Corominas Lasalle G, Puig Martorell J, González Casquet P, Bullon Chia A. Renal insufficiency and hyperkalemia in acute heart failure. Emergencias. 2018;30:357-8.

14. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88:107-15.

15. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351:543-51.

16. Adams KF Jr., Fonarow GC, Emerman CL, et al., ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209–16.

17. Michel A, Martín-Pérez M, Ruigómez A, García Rodríguez LA. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. Eur J Heart Fail. 2015;17:205-13.

18. Llorens P. Risk assessment in emergency department patients with acute heart failure: We need to reach beyond our clinical judgment. *Emergencias*. 2018;30:75-6.
19. Formiga F, Chivite D. Acute heart failure: Understanding the patient is essential. *Emergencias*. 2018;30:145-6.
20. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;169:1156 –1162.
21. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome-an analysis from RELAX-AHF. *Eur J Heart Fail* 2014;16:1230e1240.
22. ter Maaten JM, Valente MA, Metra M, Bruno N, O'Connor CM, Ponikowski P, et al. A combined clinical and biomarker approach to predict diuretic response in acute heart failure. *Clin Res Cardiol* 2016;105:145-53.
23. Tromp J, Ter Maaten JM, Damman K, O'Connor CM, Metra M, Dittrich HC et al. Serum Potassium Levels and Outcome in Acute Heart Failure (Data from the PROTECT and COACH Trials). *Am J Cardiol*. 2017;119:290-96.
24. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372:211-21.

25. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32:820 – 25.
26. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372:222–31.
27. Das S, Dey JK, Sen S, Mukherjee R. Efficacy and Safety of Patiromer in Hyperkalemia: A Systematic Review and Meta-Analysis. *J Pharm Pract*. 2018;31:6-17.
28. Mahoney BA, Smith WA, Lo D, Tsoi K, Tonelli M, Clase C. Emergency interventions for hyperkalaemia. *Cochrane Database Syst Rev*. 2005;2:CD003235.

Figure 1. Flowchart of patient inclusion in the present study. EAHFE: Epidemiology of Acute Heart Failure in Emergency departments.

Table 1. Characteristics of the global cohort and the four groups classified according to the presence or not of renal dysfunction (RD) and hyperkalaemia (Hk).

	Total (n=11935)	NoRD-NoHk (n=5088)	NoRD-Hk (n=150)	RD-NoHk (n=6012)	RD-Hk (n=685)	P value
Demographic data (n, %)						
Age (years) [†]	80.1 ± 10.1	78.0 ± 11.1	77.2 ± 11.1	81.8 ± 9.0	81.4 ± 9.6	< 0.001
Age ≥ 75 years	9040 (75.7)	3512 (69.0)	98 (65.3)	4880 (81.2)	550 (80.3)	< 0.001
Male	5324 (44.6)	2565 (50.4)	79 (52.7)	2394 (39.8)	286 (41.8)	< 0.001
Personal history (n, %)						
Arterial hypertension	10001 (84.0)	4015 (79.1)	119 (79.9)	5279 (88.0)	588 (86.0)	< 0.001
Diabetes mellitus	5053 (42.4)	1879 (37.2)	78 (52.3)	2712 (45.2)	384 (56.1)	< 0.001
Ischaemic heart disease	3452 (29.0)	1276 (25.1)	41 (27.5)	1940 (32.3)	195 (28.5)	< 0.001
Chronic kidney failure	3117 (26.2)	279 (5.5)	17 (11.4)	2494 (41.5)	327 (47.8)	< 0.001
Atrial fibrillation	5847 (49.1)	2421 (47.7)	76 (51.0)	3039 (50.6)	311 (45.5)	0.004
Peripheral artery disease	1089 (9.1)	366 (7.2)	16 (10.7)	626 (10.4)	81 (11.8)	< 0.001
Cancer	1508 (14.3)	640 (14.1)	22 (16.3)	762 (14.5)	84 (13.9)	0.844
Prior episode of heart failure	6979 (59.5)	2616 (52.4)	83 (56.8)	3848 (65.1)	432 (63.8)	< 0.001
Basal situation (n, %)						
Barthel Index < 60 points	1907 (18.2)	638 (14.4)	23 (17.8)	1100 (20.6)	146 (25.3)	< 0.001
NYHA functional class III–IV	2736 (24.5)	949 (20.0)	38 (27.7)	1554 (27.6)	195 (31.2)	< 0.001
LVEF < 40%	1397 (21.8)	518 (19.9)	23 (28.8)	762 (22.5)	94 (27.9)	0.001
Chronic treatments (n, %)						
Loop diuretics	7685 (66.5)	2872 (58.5)	83 (56.5)	4268 (73.3)	462 (69.0)	< 0.001
Thiazide diuretics	1687 (14.6)	727 (14.8)	14 (9.5)	856 (14.7)	90 (13.4)	0.264
ACEI or ARB	6638 (57.5)	2839 (57.8)	95 (64.6)	3293 (56.5)	411 (61.3)	0.023
MRA	1974 (17.1)	731 (14.9)	31 (21.1)	1048 (18.0)	164 (24.5)	< 0.001
Beta-blocker	4806 (41.6)	1899 (38.7)	68 (46.3)	2554 (43.9)	285 (42.5)	< 0.001
Nitrates	2073 (17.9)	677 (13.8)	26 (17.7)	1244 (21.4)	126 (18.8)	< 0.001
Oral anticoagulation	2168 (18.8)	920 (18.7)	34 (23.1)	1099 (18.9)	115 (17.2)	0.391
Data of the acute episode (n, %)						
Dyspnea	10824 (91.0)	4635 (91.4)	132 (89.2)	5452 (91.0)	605 (88.8)	0.135
Orthopnoea	6617 (55.7)	2781 (54.9)	79 (53.4)	3361 (56.1)	396 (58.2)	0.271
Oedema	8068 (67.8)	3328 (65.6)	99 (66.9)	4162 (69.5)	479 (70.3)	< 0.001
O ₂ saturation ≤ 90%	3233 (28.1)	1312 (26.7)	47 (32.9)	1631 (28.1)	243 (37.1)	< 0.001
SBP ≤ 100 mmHg	650 (5.5)	180 (3.6)	12 (8.2)	382 (6.4)	76 (11.4)	< 0.001
Hyponatremia (<135 mmol/l)	2175 (18.3)	860 (17.0)	55 (36.7)	1019 (17.1)	241 (35.5)	< 0.001
Potassium (mmol/L) [†]	4.42 ± 0.69	4.19 ± 0.51	6.04 ± 0.86	4.39 ± 0.54	6.00 ± 0.60	< 0.001
Creatinine (mg/dl) [†]	1.36 ± 0.85	0.85 ± 0.19	0.90 ± 0.18	1.70 ± 0.90	2.19 ± 1.21	< 0.001
eGFR (ml/min/m ²) [†]	59.10 ± 27.65	84.15 ± 20.71	79.05 ± 17.89	40.45 ± 12.54	32.34 ± 13.10	< 0.001
Treatment in ED (n, %)						
Need for oxygen	8631 (73.1)	3650 (72.5)	105 (70.0)	4379 (73.6)	497 (73.5)	0.450
Need for intravenous diuretics ‡	10214 (86.7)	4326 (86.1)	131 (87.3)	5163 (87.0)	594 (88.0)	0.345
Need for intravenous nitrates	1815 (15.4)	754 (15.0)	29 (19.3)	932 (15.7)	100 (14.8)	0.390
Need for inotropic or vasopressor	237 (2.0)	53 (1.1)	7 (4.7)	128 (2.2)	49 (7.3)	< 0.001
Need for morphine	644 (6.1)	238 (5.3)	11 (8.1)	333 (6.4)	62 (10.3)	< 0.001
Need for non-invasive ventilation	821 (7.0)	271 (5.4)	14 (9.3)	430 (7.2)	106 (15.7)	< 0.001
Need for invasive ventilation	315 (2.7)	138 (2.7)	3 (2.0)	157 (2.6)	17 (2.5)	0.930
Evolutive data (n, %)						
Hospital admission	9013 (75.6)	3647 (71.7)	118 (78.7)	4653 (77.5)	595 (86.9)	< 0.001
Stay (days) [†]	7.7 ± 12.3	6.9 ± 10.4	9.9 ± 25.5	8.1 ± 12.4	9.6 ± 18.1	< 0.001

[†]Values are mean ± SD, n (%). RD: renal dysfunction. Hk Hyperkalaemia. Chronic kidney failure (creatinine > 2mg/dl), NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. SBP: Systolic blood pressure. ED: emergency department. eGFR: estimated glomerular filtration rate, calculated with the formula MDRD-4 (Modification of Diet in Renal Disease). ‡ Use of loop diuretics in perfusion, in bolus or both.

Table 2. Crude and adjusted Hazard Ratios (HR) for the different groups based on the presence of renal dysfunction (RD) and hyperkalaemia (Hk) during the episode of acute heart failure.

	Crude HR (CI 95%)	P value	Adjusted HR (CI 95%)	P value
Primary endpoint				
30-day all-cause mortality				
NoRD-NoHk	reference		reference	
NoRD-Hk	2.06 (1.31 – 3.23)	0.002	1.17 (0.51 – 2.69)	0.714
RD-NoHk	1.64 (1.44 – 1.87)	< 0.001	1.34 (1.04 – 1.71)	0.022
RD-Hk	4.23 (3.52 – 5.07)	< 0.001	2.44 (1.67 – 3.55)	< 0.001
Secondary endpoint				
In-hospital all-cause mortality				
NoRD-NoHk	reference		reference	
NoRD-Hk	1.21 (0.74 – 1.97)	0.455	0.98 (0.40 – 2.40)	0.996
RD-NoHk	1.04 (0.89 – 1.21)	0.641	0.95 (0.70 – 1.29)	0.747
RD-Hk	1.31 (1.07 – 1.62)	0.010	0.95 (0.61 – 1.49)	0.831
30-day ED reconsultation for HF				
NoRD-NoHk	reference	-	reference	
NoRD-Hk	1.22 (0.85 – 1.75)	0.275	0.86 (0.47 – 1.57)	0.621
RD-NoHk	1.27 (1.17 – 1.38)	< 0.001	1.06 (0.92 – 1.23)	0.422
RD-Hk	1.35 (1.13 – 1.61)	0.001	1.06 (0.78 – 1.45)	0.703
30-day all-cause death or ED reconsultation for HF				
NoRD-NoHk	reference	-	reference	
NoRD-Hk	1.43 (1.08 – 1.91)	0.014	1.00 (0.62 – 1.63)	0.996
RD-NoHk	1.34 (1.25 – 1.44)	< 0.001	1.08 (0.95 – 1.23)	0.223
RD-Hk	2.01 (1.78 – 2.29)	< 0.001	1.33 (1.04 – 1.70)	0.021

Adjusted: male, age ≥ 75 years, personal history of arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic kidney failure, atrial fibrillation, peripheral artery disease or prior episode of heart failure; basal situation with Barthel Index < 60 points, NYHA functional class III–IV or left ventricular ejection fraction $< 40\%$; chronic treatments with loop diuretics, angiotensin-converter enzyme inhibitor or angiotensin receptor blocker, mineralocorticoid receptor antagonist, beta-blocker or nitrates; acute episode with oedema, O₂ saturation $\leq 90\%$, systolic blood pressure ≤ 100 mmHg or hyponatremia (sodium < 135 mmol/l); need in emergency department of inotropic or vasopressor, morphine or non-invasive ventilation, and hospital admission.

Figure 2. Survival curve adjusted for the primary endpoint (30-day all-cause mortality) in the different study groups.

Figure 3. Stratified analysis of the adjusted hazard ratios (HR) for primary endpoint (30-day all-cause mortality) the different groups based on the presence of renal dysfunction (RD), hyperkalaemia (Hk) or both during the episode of acute heart failure (reference group NoRD-NoHk).

RD: renal dysfunction. Hk Hyperkalaemia. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. nc: not calculated, because the sample size does not allow it.

Figure(s)
[Click here to download high resolution image](#)

Figure(s)

[Click here to download high resolution image](#)

Figure(s)
[Click here to download high resolution image](#)

Figure 3. Stratified analysis of the adjusted hazard ratios (HR) for primary endpoint (30-day all-cause mortality) the different groups based on the presence of renal dysfunction (RD), hyperkalaemia (Hk) or both during the episode of acute heart failure (reference group NoRD-NoHk).

RD: renal dysfunction. Hk Hyperkalaemia. LVEF: Left ventricular ejection fraction. ACEI: angiotensin-converter enzyme inhibitor. ARB: angiotensin receptor blocker. MRA: Mineralocorticoid receptor antagonist. nc: not calculated, because the sample size does not allow it.

Supplementary material.

Table 1. Values of beta coefficients in multivariate analysis.

	Primary endpoint	Secondary endpoint		
	30-day all-cause mortality	In-hospital all-cause mortality	30-day ED reconsultation for HF	30-day all-cause death or ED reconsultation for HF
Demographic data (n, %)				
Age ≥ 75 years	0.665	0.404	0.056	0.184
Male	0.005	0.119	0.157	0.138
Personal history (n, %)				
Arterial hypertension	-0.212	- 0.016	0.012	-0.012
Diabetes mellitus	0.033	- 0.004	0.024	- 0.001
Ischaemic heart disease	0.101	0.183	- 0.026	0.012
Chronic kidney failure	0.030	- 0.005	0.044	0.029
Atrial fibrillation	0.024	0.354	0.017	-0.002
Peripheral artery disease	-0.155	- 0.174	- 0.046	- 0.067
Prior episode of heart failure	0.221	0.127	0.306	0.276
Basal situation (n, %)				
Barthel Index < 60 points	0.832	0.272	0.223	0.419
NYHA functional class III–IV	0.317	0.052	0.209	0.240
LVEF < 40%	0.218	0.152	- 0.173	- 0.062
Chronic treatments (n, %)				
Loop diuretics	0.120	- 0.009	0.240	0.222
ACEI or ARB	-0.447	- 0.154	- 0.112	- 0.193
Aldosterone antagonist	0.058	0.129	0.081	0.074
Beta-blocker	-0.238	- 0.117	- 0.022	- 0.070
Nitrates	0.061	- 0.137	0.164	0.096
Data of the acute episode (n, %)				
Oedema	-0.019	- 0.055	0.062	0.036
O2 saturation ≤ 90%	0.106	0.101	- 0.049	0.000
SBP ≤ 100 mmHg	0.748	0.272	0.375	0.472
Hyponatremia (<135 mmol/l)	0.422	0.102	0.233	0.275
Treatment in ED (n, %)				
Need for inotropic or vasopressor	0.233	-0.259	0.337	0.337
Need for morphine	1.085	0.595	0.245	0.621
Need for non-invasive ventilation	0.125	- 0.039	- 0.073	- 0.031
Evolutive data (n, %)				
Hospital admission	0.500	- 0.902	- 0.228	- 0.101

Acute heart failure and adverse events associated with the presence of renal dysfunction and hyperkalaemia. EAHFE- Renal Dysfunction and Hyperkalaemia

Javier Jacob. Emergency Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Catalonia, Spain.

Lluís Llauger. Emergency Department, Hospital Universitari de Vic, Barcelona, Spain.

Pablo Herrero-Puente. Emergency Department, Hospital Universitario Central de Asturias, Oviedo. Spain.

Francisco Javier Martín-Sánchez. Emergency Department, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC); Facultad de Medicina, Universidad Complutense, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid. Spain.

Pere Llorens. Emergency Department, Short-Stay Unit and Home Hospitalization, Hospital General de Alicante. Spain.

Alex Roset. Emergency Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Catalonia, España.

Victor Gil. Emergency Department, Hospital Clínic, University of Barcelona. Barcelona, Catalonia, Spain.

Marta Fuentes. Emergency Department. Hospital Universitario de Salamanca. Salamanca. Spain.

Francisco Javier Lucas-Imbernón. Emergency Department. Hospital General Universitario de Albacete. Spain.

Òscar Miró
Emergency Department, Hospital Clínic, University of Barcelona. Barcelona, Catalonia, Spain.

ICASEMES-RESEARCH GROUP

Address for correspondence:

Lluís Llauger. Emergency Department, Hospital Universitari de Vic.
Francesc Pla el Vigatà 1. Vic. 08500 Vic. Barcelona.

e-mail: llauger.doc@gmail.com

Telephone: +34 938 89 11 11

Members Of the ICA-SEMES Research Group. Marta Fuentes, Cristina Gil (Hospital Universitario de Salamanca), Héctor Alonso, Enrique Pérez-Llantada (Hospital Marqués de Valdecilla de Santander), Guillermo Llopis García, María Carmen Santos Matallana, María Luisa Docavo Barrenechea-Moxó, Lucía Salgado Pérez (Hospital Clínico San Carlos de Madrid), Rosa Escoda, Carolina Xipell, Carolina Sánchez, Josep María Gaytan (Hospital Clínic de Barcelona), María José Pérez-Durá, Eva Salvo (Hospital Politènic La Fe de Valencia), José Pavón (Hospital Dr. Negrín de Las Palmas de Gran Canaria), Antonio Noval (Hospital Insular de Las Palmas de Gran Canaria), José Manuel Torres (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 (Consorti Sanitari de Terrassa), Susana Sánchez Ramón, Virginia Carbajosa Rodríguez (Hospital Universitario Río Hortega de Valladolid), Pascual Piñera, José Andrés Sánchez Nicolás (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), Alex Roset, Irene Cabello, Antonio Haro (Hospital Universitari de Bellvitge de Barcelona), Fernando Richard, José María Álvarez Pérez, María Pilar López Díez (Hospital Universitario de Burgos), Joaquín Vázquez Álvarez, Belén Prieto García, María García García, Marta Sánchez González (Hospital Universitario Central de Asturias de Oviedo), Patricia Javaloyes, Víctor Marquina, Inmaculada Jiménez, Néstor Hernández, Benjamín Brouzet, Begoña Espinosa (Hospital General 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 (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 Infanta Leonor de Madrid), José Luis Carballo (Complejo Hospitalario Universitario de Ourense), Esther Rodríguez-Adrada, Belén Rodríguez Miranda (Hospital Rey Juan Carlos de Móstoles de Madrid).

Financial support:

This study was partially supported by competitive grants from the Instituto de Salud Carlos III supported with funds from the Spanish Ministry of Health and FEDER (PI10/01918, PI11/01021, PI15/01019, PI15/00773, PI18/00393, PI18/00456), Catalonia Government (SGR 2009/1385, 2014/0313, 2017/1424), and Fundació La Marató de TV3 (2015/2510). The ICA-Research Group has received unrestricted funding from Novartis and Orion Pharma. The design of the study, patient inclusion, data analysis, discussion and final conclusions were exclusively carried out by the authors with no participation of the granters.

Conflict of Interest Disclosure:

JJ reports no conflict of interest.

LLL reports no conflict of interest.

PHP reports no conflict of interest.

FJMS reports no conflict of interest.

PLL reports no conflict of interest.

AR reports no conflict of interest.

VG reports no conflict of interest.
MF reports no conflict of interest.
FJLI reports no conflict of interest.
OM reports no conflict of interest.

Key Words

Acute heart failure, renal dysfunction, hyperkalaemia, prognosis, EAHFE

Highlights (mandatory)

Highlights consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). See the following website for more information

<http://www.elsevier.com/highlights>

The presence of renal dysfunction and hyperkalemia is common in patients with acute heart failure.

The combination of both is associated with more 30-day all-cause mortality.

This combination was not related to more in-hospital all-cause mortality.

This combination was not related to more 30-day ED reconsultation for HF.