Time-pattern of adverse outcomes after an infection-triggered acute heart failure decompensation and the influence of early antibiotic administration and hospitalisation. Results of the PAPRICA-3 study

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ABSTRACT (300 words)

Objective: To investigate whether patients with an acute heart failure (AHF) episode triggered by infection present different outcomes compared to patients with no trigger, with specific analysis of the time pattern for these hypothetical differences, and the effects of early antibiotic administration (EAA) and hospitalisation.

Methods: This is a secondary analysis of the EAHFE Registry, which includes consecutive AHF patients diagnosed in 41 emergency departments. We made two groups according to the AHF trigger: infection (G1) or none identified (G2). The primary outcome was 13-week (91-days) all-cause mortality, and secondary outcomes were 13-week post-discharge mortality, readmission or combined endpoint. Comparisons are presented as unadjusted and adjusted (MEESSI risk score) hazard ratios (uHR/aHR) for G1 compared to G2 patients, also estimated by weeks. Stratified analysis by EAA (provided/not provided) and patient disposition (discharged/hospitalized) was performed.

Results: We included 6727 patients (G1=3973; G2=2754), aged 81(10) years, 54.3% females. The 13-week mortality uHR was 1.11 (0.99-1.25; $p=0.06$; with significant increases in the first 3 weeks), and the aHR was 0.91 (0.81-1.02; $p=0.11$). There were no differences in unadjusted secondary post-discharge outcomes (with only a significant increase in the risk of death in week 2); however, G1 outcomes significantly improved after adjustment: aHRs 0.83 (0.71-0.96; $p=0.01$) for mortality (although an increased risk was present at week 2), 0.92 (0.84-0.99; $p=0.04$) for readmission, and 0.92 (0.85-0.99; $p=0.04$) for combined endpoint. We found a differentiated effect of hospitalisation ($p<0.05$ for interaction; better post-discharge readmission and combined outcomes in G1); and a trend ($p=0.06$) to lower mortality for G1 patients with EAA.

Conclusion: AHF triggered by infection is not associated with a higher mid-term mortality, and has better post-discharge outcomes; however, the first 3 weeks are an extremely vulnerable period. In this group of patients, hospitalisation limits the risk of adverse post-discharge events, and EAA probably reduces mortality.

INTRODUCTION

Acute heart failure (AHF) is still associated with a high mortality, estimated at around 10% and 30% at one month and one year after decompensation, respectively^{1,2}. Successive attempts to improve outcomes with the use of new drugs have failed³⁻⁵. In this scenario, efforts have been aimed at paying greater attention to the prehospital phase⁶⁻⁸ to better manage the comorbidities and patient frailty frequently associated with AHF^{9,10} in order to improve decision-making with respect to discharge after both emergency department care and hospitalisation^{11,12}, and to provide more adequate post-discharge transitional plans to protect patients during the vulnerable phase^{13,14}. In this sense, the importance of recognizing and treating factors triggering a decompensation of AHF has been increasingly underlined. Based on a recent systematic review, triggers have been recognized in at least 50% of patients in all the previously published series, the most frequent being dietetic/therapeutic transgression, acute coronary syndrome, tachyarrhythmia and infection¹⁵. Very recently, Arrigo *et al.* reported that each trigger can have a specific and different time pattern which can influence patient outcomes (conferring either protection or hazard)¹⁶. Accordingly, the current recommendations of the European Society of Cardiology (ESC) guidelines for the management of AHF advise early recognition and treatment of triggering factors, since they may have an impact on prognosis after an AHF decompensation¹⁷.

Taking this into account, infection is one of the triggers most frequently involved in AHF episodes, and leads the list of triggers in many series¹⁵. However, the relative frequency of infection is very heterogeneous, especially depending on the setting in which the patients were recruited. Indeed, the frequency can range from as high as the 58% observed in AHF patients hospitalised in internal medicine wards¹⁸ to only the 6% reported in AHF patients hospitalised in a cardiology department¹⁹⁻²⁰. There are also discrepancies in the influence of infection on mortality; while some authors have reported infection to have no impact^{21,22}, others have described an increased risk of death, especially during hospitalisation and the first 2 to 4 weeks after decompensation, in comparison with patients with no identified trigger^{15,23}. On the other hand, the relationship between infection and the risk of readmission has been poorly explored, and only one previous study has suggested that infection has no influence on the development of AHF²². Finally, the study setting of these studies was one of the main limitations against obtaining strong conclusions, since most only included AHF patients attended in a particular hospital ward by a particular medical team.

Bearing in mind all the above mentioned discrepancies and limitations, we aimed to evaluate the influence of infection as a trigger of an AHF episode on outcomes (not only limited to the risk of death) in consecutive patients diagnosed at emergency departments (ED). This setting was chosen in order to be as close as possible to the whole universe of patients with AHF. We were also especially interested in determining the time point at which the potential differences in risk occur. Finally, we investigated if early antibiotic administration (EAA) and patient disposition after ED care (discharge/admission) influence the outcomes of patients with an AHF episode triggered by infection.

MATERIAL AND METHODS

Setting

The PAPRICA-3 (apocope from the Spanish words *PApel del los PREcipitantes de episodios de Insuficiencia Cardíaca Aguda*; in English: Role of precipitants of AHF) study was designed as an exploratory, secondary analysis within the EAHFE Registry. The EAHFE Registry was initiated in 2007 and every 2-3 years carries out a 1-2-month recruitment period of all consecutive patients diagnosed with AHF in Spanish EDs participating in the project. To date, 5 recruitment phases (2007, 2009, 2011, 2014, and 2016) have been performed with the participation of 41 EDs from community and university hospitals across Spain (representing about 13% of the Spanish public health care system hospitals), enrolling a total of 13,791 AHF patients. The PAPRICA-3 study included data of the 11,360 patients recruited in phases 3 to 5, since data on triggers of the AHF episode or data of readmission were not recorded in phases 1 and 2. Details of patient inclusion have been reported previously^{2,11}. Briefly, patient enrolment is done by any attending emergency physician in the participating EDs, who receives specific study protocol instructions during a weekly ED meeting preceding patient recruitment. These physicians are responsible for the detection of potential cases of AHF. All suspected cases are confirmed by the principal investigator of each centre to ensure the patients meet the diagnostic criteria of AHF based on the Framingham clinical criteria²⁴. If possible, the diagnosis is also confirmed by measurement of plasma natriuretic peptide and/or echocardiography during ED or hospital stay following the current ESC guideline recommendations¹⁷. The principal investigator of each centre is responsible for the final diagnostic adjudication of the cases. The only exclusion criterion for being included into the EAHFE Registry is a primary diagnosis of ST-elevation myocardial infarction (STEMI) while concurrently developing AHF (which occurs in about 3% of AHF cases), as the majority of these patients bypass the ED and go directly to the catheterization laboratory. The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions. However, all of these physicians are aware of the ESC guidelines, which are the main reference for all emergency physician actions.

Ethics

The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, and 160/15. Due to the non-interventional design of the registry, Spanish legislation allows central Ethical Committee approval, accompanied by notification to the local Ethical Committees. All participating patients gave informed consent to be included in the registry and to be contacted for follow up. The PAPRICA-3 study was carried out in strict compliance with the Declaration of Helsinki principles. The authors designed the study, gathered, and analysed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

Design and variables recorded

Patients with a final diagnosis of AHF in whom data regarding the presence of a trigger was recorded were considered for the analysis. The PAPRICA-3 study was designed to compare the outcomes of patients in whom an active infection was identified as being the precipitant factor of the AHF episode with the outcomes of patients in whom no precipitant was identified after

extensive review of the clinical and complementary data of the episode. Adjudication of a trigger for the current episode of AHF was not performed centrally, but rather was proposed by the attending physicians and revised by the principal investigator of each centre, who was responsible for the final patient classification. In the case of infection, the adjudication was done based on the presence of signs and symptoms of active infection, regardless of the site of infection, during 7 days prior to AHF diagnosis, in conjunction with a congruent temporal pattern with respect with the development of signs and symptoms of heart failure. The only exclusion criterion was the absence of follow-up for mortality, as this was the primary outcome evaluated in the present study (see below). Thirty-three independent variables were recorded, including demographic data (2 variables), comorbidities (10 variables), baseline status (3 variables), chronic treatments for heart failure (5 variables), vitals at ED arrival (3 variables) and analytical data in the ED (8 variables) (see [Supplemental Table 1](#) for definitions). In order to adjust for the severity of AHF episode, we calculated the MEESI risk score for every patient. This risk score has recently been reported to accurately estimate the risk of death during the following 30 days in patients diagnosed with AHF in the ED^{11,25}.

Outcomes

The 13-week (91 days) all-cause mortality was the primary endpoint evaluated in the PAPRICA-3 study. As secondary endpoints, we recorded three main post-discharge outcomes, which were calculated for patients discharged alive from the hospital (in-hospital deaths were not included among these outcomes). They consisted in the 13-week post-discharge all-cause death, 13-week post-discharge readmission due to AHF, and 13-week post-discharge combined endpoint. Follow-up was performed through telephone contact and consultation of primary care and hospital medical records. Adjudication of events was made at an at-site level by the principal investigator of each centre participating in the study.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed, and discrete variables as absolute values and percentages. Comparison among groups was carried out using one-way ANOVA or the Mann-Whitney non-parametric test for continuous variables and the chi square test for discrete variables. Kaplan-Meier curves were plotted for both groups of patients and were compared by means of the log-rank test. The risk of having primary and secondary outcomes in patients with an AHF episode triggered by infection compared to those with no trigger was expressed by a hazard ratio (HR) calculated by Cox regression, first unadjusted and then adjusted for the MEESI risk score. An analysis of interaction was made according to the stratification of patients based on EAA (considered to be present if a systemic antibiotic had been taken before ED consultation or was administered during ED stay) and disposition after ED care (hospitalisation or direct discharge home). We conducted exploratory analyses of the variation in relative HR of primary and secondary outcomes among those still alive in the cohort by time since admission. Following the same analytical strategy as Arrigo *et al.*¹⁶, we used a maximally flexible approach to allow the HRs to vary over time. We divided the cohort into seven time periods, roughly balancing even numbers of events without being completely arbitrary: weekly for the first 4 weeks, then biweekly for the next 4 weeks, then combining the remaining weeks of the cohort, and

estimating separate HRs for each time period. In addition, all these time point calculations were repeatedly adjusted for the MEESi score. Since this was an exploratory analysis to interpret several different questions, no adjustment for multiple comparisons was made, because each question implies different numbers of comparisons, and therefore, standard confidence intervals (CIs) are reported and interpreted cautiously. In addition, due to the exploratory nature of our investigation, a pre-hoc sample size calculation was not made. Statistical significance was accepted if the 95% CI of the HRs excluded the value 1, or the p value was less than 0.05.

RESULTS

Of the 11,360 patients included in the EAHFE registry in phases 3 to 5, in the present analysis we included 6,727 patients for whom the primary outcome was recorded: 3973 corresponded to patients with an AHF episode triggered by an infection, and 2754 in which no trigger was identified (**Figure 1**). Overall, the patients were 81(10) years of age, 54.3% were female, and comorbidities were highly prevalent (the most frequent being hypertension, atrial fibrillation, diabetes mellitus, ischaemic cardiomyopathy, heart valve disease, chronic kidney disease, and chronic obstructive pulmonary disease). More than half of the patients had had previous episodes of AHF. The remaining patient characteristics are shown in **Table 1** and, as can be seen, the two groups of patients differed in 16 out of the 33 characteristics. The median MEESSE risk score for the whole population was -2.8 points (IQR -3.6 to -2.0), and it was significantly higher ($p<0.001$ by non-parametric Mann-Whitney test) in patients with infection (median -2.6, IQR -3.4 to -1.7) than in patients with no trigger (median -3.0, IQR -3.7 to -2.1), indicating that the former group had a higher risk of death during the AHF episode.

The overall 13-week mortality was 11.0%, and the unadjusted HR for patients with infection was 1.11 (0.99-1.25; $p=0.06$) (**Figure 2**). On analysing the risk for individual time periods, we observed that this increase in mortality was restricted to the first three weeks (**Figure 3**). With respect to secondary endpoints, the 13-week post-discharge mortality, readmission and combined endpoint were 5.5%, 25.9% and 28.1% for the whole cohort, respectively, with an unadjusted HR for patients with infection of 0.97 (0.84-1.12; $p=0.69$), 0.95 (0.87-1.12; $p=0.26$) and 0.97 (0.89-1.05; $p=0.44$), respectively (**Figure 2**). Time-point analysis only detected a significant increase in mortality in patients with infection during week 2 after discharge (**Figure 3**).

After adjustment of outcomes for the severity of patient decompensation (estimated by the MEESSE risk score), there was no difference in the primary endpoint (aHR 0.91; 0.81-1.02; $p=0.11$) (**Figure 2**), with no statistically significant difference at any time point (**Figure 3**). On the other hand, patients with infection as the trigger showed better secondary outcomes after adjustment; with 13-week post-discharge aHRs of 0.83 (0.71-0.96; $p=0.01$) for mortality, 0.92 (0.84-0.99; $p=0.04$) for readmission, and 0.92 (0.85-0.99; $p=0.04$) for the combined endpoint (**Figure 2**). Nonetheless, the excess in post-discharge mortality risk in week 2 observed in unadjusted analyses still remained statistically significant after adjustment (**Figure 3**).

The stratified analysis showed a differentiated effect for patient disposition, with hospitalisation providing better post-discharge readmission (p for interaction 0.04) and combined endpoint (p for interaction 0.04) outcomes. On the other hand, EAA was systematically associated with better results for patients with infection compared to patients without a trigger in all the outcomes assessed, although this interaction did not achieve statistical significance for any outcome (**Figure 4**).

DISCUSSION

The PAPRICA-3 study evaluated the effect of the presence of an infection triggering an episode of AHF in a large cohort of patients recruited at the ED. This fact minimises the bias of selecting only patients managed by a particular hospital department. The study focused not only on mid-term mortality, but also on all-cause mortality and the risk of readmission after discharge following an index AHF episode. In addition, this study performed a more in depth evaluation of the time pattern during which a potential increase in risk caused by infection happens; an aspect which has been poorly explored to date. Finally, the potential effect of EAA and hospitalisation, two factors that can modify outcomes, has also been investigated. The 3 main findings reported by the PAPRICA-3 study are discussed below.

The first conclusion of our work is that, although patients with an AHF decompensation triggered by an infection seem to have a higher risk of death during the following 13 weeks, this apparent increased risk of death disappears after adjustment for confounding factors. This indicates that probably the risk associated with the patients' characteristics and severity of the AHF episode is more important determinants of mortality than the infection itself. However, it is important to note that the first 3 weeks after ED decompensation are responsible for this apparent increase in mortality. Therefore, although AHF triggered by infection is not associated with an overall higher mid-term mortality, the first 3 weeks after the episode is a highly vulnerable period. This finding indicates the highest risk period during which clinicians should maintain a closer follow-up in order to improve patient outcomes. Indeed, even though there was no increase in mortality after adjustment, closer follow-up of patients during these first 3 weeks post-AHF might even lead to a better mid-term survival (13 weeks) in patients with infection-triggered AHF episodes compared to those with no identified trigger.

The second finding is that infection-triggered AHF decompensations have better post-discharge outcomes than AHF with no identified trigger. The presence of a cardiomyopathy non-related factor sensitive to correction likely makes it easier to apply a specific treatment (antibiotic) to these patients, which otherwise could not be done in AHF patients with unknown precipitants. Following reports of AHF patients being in a vulnerable phase following discharge¹³, researchers have been paying increasing attention to outcomes after patient discharge following the index event. Indeed, actions addressed to this period could provide enormous benefits. A very recent meta-analysis of 41 randomised trials testing transitional care interventions demonstrated that implementation of transitional plans at AHF patient discharge achieves a significant reduction of 8% and 29% in the risk of rehospitalisation and ED visits, respectively²⁵. In addition, another recent meta-analysis described the benefits of heart failure clinics in reducing hospitalisation for AHF and all-cause mortality, which was greater among patients with recent ED visit or hospitalisation due to decompensation²⁶. Again, time-point analysis of risks provides a key post-discharge outcome improvement, as it showed that during the second week after discharge there is a significant increase in mortality, which remains even after model adjustment. Although the PAPRICA-3 study was not designed to investigate the causes of this increment in death at this time point, we believe that close monitoring shortly after discharge is mandatory in these patients in order to improve the current patient outcomes.

Finally, stratified analysis suggests that EAA and especially hospitalisation can have benefits in infection-triggered AHF decompensations. Although the administration of EAA did not show statistical significance, it was always associated with better HRs (and in the case of mortality this trend was close to statistical significance, with a *p* for interaction of 0.06) than in patients not receiving antibiotics before or during ED care. In this latter group of patients, it is foreseeable (although we did not check this) that an antibiotic was provided during hospital admission or prescribed to take at home if the patient was discharged directly from the ED. Therefore, the absence of EAA does not necessarily equate with an absence of antibiotic treatment, and this fact has probably diluted the differences in outcomes found in the stratified analysis by EAA. Nonetheless, what seems to be more relevant and statistically significant is the relationship between hospitalisation and improved post-discharge outcomes in patients with an infection-triggered AHF episode, especially the reduction of readmissions. Some authors have highlighted the increased risks for AHF patients entirely managed at the ED and discharged home without hospitalisation^{12, 27-29}, and the PAPRICA-3 findings highlight that this is true in AHF patients with infection. Although our results were obtained with a *post-hoc* subanalysis, we believe that direct discharge from the ED home in this subgroup of patients with AHF and concurrent infection should be made with extreme caution.

Our study has some limitations. First, this is a secondary analysis limited to hypothesis generation that requires confirmation in future trials. Second, since there was no sample size calculation due to the exploratory nature of the study, a type-II error cannot be excluded in some of the estimations made, especially in subgroup comparisons, in which fewer outcomes were taken into account – o – were included. Third, this a real life cohort, without intervention, and attending emergency physicians did not receive any specific instructions about patient management and disposition. Therefore, the exact indication for antibiotic administration is not known, and it was not possible to differentiate between bacterial and viral infections. Fourth, the diagnosis of AHF was based on clinical criteria, and in all the cases the final diagnosis of AHF was not supported by natriuretic peptide or echocardiographic criteria. The same occurs with respect to the definition of infection and its adjudication as a trigger of the AHF episode. Fifth, the patients were from a single country, and therefore, external validation of our results should be made by further studies in other countries. And sixth, data regarding site of infection, the kind of antibiotic used and duration of treatment, and how many patients deteriorated into septic shock were not recorded. Accordingly, we cannot infer the role of all these factors in our findings.

Despite all these limitations, we believe that the data obtained in the PAPRICA-3 study, which includes a large registry of consecutive cases of AHF diagnosed in the ED, strongly suggest that the co-existence of an infection is not, by itself, associated with a worse prognosis during an episode of AHF, and post-discharge outcomes could be even better than in patients with no trigger for the AHF episode. Additionally, the study pinpoints areas for outcome improvement, highlighting the need for closer follow-up during the first few weeks after the index episode and after patient discharge in order to reduce the risk of death, as well as hospitalisation in order to avoid post-discharge readmissions due to AHF.

REFERENCES

- 1.- Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017; 19:1242-1254
- 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.- O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med.* 2011; 365:32-43.
- 4.- Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. Effect of Ularitide on Cardiovascular Mortality in Acute Heart Failure. *N Engl J Med.* 2017; 376:1956-1964.
- 5.- European Society of Cardiology. Serelaxin fails to meet primary endpoints in phase 3 RELAX-AHF-2 trial. Accessed: 30/09/2018. Available at: <https://www.escardio.org/The-ESC/Press-Office/Press-releases/serelaxin-fails-to-meet-primary-endpoints-in-phase-3-relax-ahf-2-trial>
- 6.- Miró O, Llorens P, Escalada X, Herrero P, Jacob J, Gil V, et al. Analysis of the different factors of prehospital care for patients with acute heart failure in Spain. The SEMICA study. *Emergencias* 2017; 29:223-230.
- 7.- Harjola P, Tolonen J, Boyd J, Mattila J, Koski R, Palomäki A, et al. The role of pre-hospital management in acute heart failure. *Eur J Heart Fail.* 2017;19:287-289.
- 8.- Harjola P, Harjola V-P. Can we do more for patients with acute heart failure before arrival at the hospital? *Emergencias* 2017:28–32.
- 9.- Formiga F, Moreno-Gonzalez R, Chivite D, Franco J, Montero A, Corbella X. High comorbidity, measured by the Charlson Comorbidity Index, associates with higher 1-year mortality risks in elderly patients experiencing a first acute heart failure hospitalization. *Aging ClinExp Res.* 2018; 30:927-933.
- 10.- Martín-Sánchez FJ, Christ M, Miró Ò, Peacock WF, McMurray JJ, Bueno H, et al. Practical approach on frail older patients attended for acute heart failure. *Int J Cardiol.* 2016; 222:62-71
- 11.- 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.
- 12.- 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.
- 13.- Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol.* 2015; 12:220-9.

- 14.- Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, et al. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail.* 2014;1:110-145.
- 15.- Aguirre Tejedó A, Miró O. Precipitating factors in acute heart failure: a review. *Emergencias.* 2017; 29:185-93.
- 16.- Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, et al. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail.* 2017; 19:201-208.
- 17.- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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; 37:2129-200.
- 18.- Moraes P, Fonseca C, Marques F, Ceia F, Aleixo A. Acutely decompensated heart failure: characteristics of hospitalized patients and opportunities to improve their care. *Rev Port Cardiol.* 2006; 25:13-27.
- 19.- Pinho Gomes AC, Silva J, Azevedo LF, Almeida R, Pinho T, Maciel MJ. Characterization of acute heart failure hospitalizations in a Portuguese cardiology department. *Rev Port Cardiol.* 2013; 32:567-75.
- 20.- Liaqat A, Moshin N, Imtiaz A, Mahreen F, Nusrat N. Factors precipitating acute heart failure. *Ann Pak Inst Med Sci.* 2014; 10:33-8.
- 21.- Hermida A, Pazo M, de la Fuente R, Lado FL, Hernández L, Rodríguez I; grupo SÁNTICOR. Epidemiological events related to decompensated heart failure. *An Med Interna.* 2008; 25 256-61.
- 22.- Miró O, Aguirre A, Herrero P, Jacob J, Martín-Sánchez FJ, Llorens P. PAPRICA-2 study: Role of precipitating factor of an acute heart failure episode on intermediate term prognosis. *Med Clin (Barc).* 2015; 145:385-9.
- 23.- Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al; for the OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes. *Arch Intern Med.* 2008; 168:847-54.
- 24.- Ho KKL, 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.
- 25.- Vedel I, Khanassov V. Transitional care for patients with congestive heart failure: a systematic review and meta-analysis. *Ann Fam Med.* 2015; 13:562-71.
- 26.- Gandhi S, Mosleh W, Sharma UC, Demers C, Farkouh ME, Schwalm JD. Multidisciplinary heart failure clinics are associated with lower heart failure hospitalization and mortality: systematic review and meta-analysis. *Can J Cardiol.* 2017; 33:1237-1244.27.

- 27.- Lee DS, Schull MJ, Alter DA, Austin PC, Laupacis A, Chong A, et al. Early deaths in patients with heart failure discharged from the emergency department: a population-based analysis. *Circ Heart Fail*. 2010; 3:228-235.
- 28.-Miró Ò, Gil V, Xipell C, Sánchez C, Aguiló S, Martín-Sánchez FJ, et al. IMPROV-ED study: outcomes after discharge for an episode of acute-decompensated heart failure and comparison between patients discharged from the emergency department and hospital wards. *Clin Res Cardiol*.2017; 106:369-378.
- 29.-Formiga F, Chivite D. Acute heart failure: Understanding the patient is essential. *Emergencias*.2018;30:145-6.

Table 1: Characteristics of the patients included in the PAPRICA-3 study and comparison depending whether the acute heart failure episode was triggered by an infection or no trigger was identified.

	Total N=6,727 n (%)	Missing values n (%)	Trigger: INFECTION N=3,973 n (%)	Trigger: NONE IDENTIFIED N=2,754 n (%)	p value
Demographic data					
Age (years) (mean (SD))	81.1 (9.7)	3 (0.0)	81.9 (9.3)	80.1 (10.1)	<0.001
Female	3,642 (54.3)	25 (0.4)	2,177 (55.0)	1,465 (53.4)	0.18
Comorbidities					
Hypertension	5,664 (84.2)	4 (0.1)	3,377 (85.0)	2,287 (83.1)	0.04
Diabetes mellitus	2,788 (41.5)	6 (0.1)	1,636 (41.2)	1,152 (41.9)	0.57
Ischaemic heart disease	1,972 (29.3)	4 (0.1)	1,139 (28.7)	833 (30.3)	0.16
Heart valve disease	1,795 (26.7)	4 (0.1)	1,005 (25.3)	790 (28.7)	0.002
Atrial fibrillation	3,363 (50.0)	3 (0.0)	2,012 (50.6)	1,351 (49.1)	0.22
Chronic kidney failure (creatinine>2 mg/mL)	1,894 (28.2)	4 (0.1)	1,132 (28.5)	762 (27.7)	0.48
Cerebrovascular disease	900 (13.4)	5 (0.1)	540 (13.6)	360 (13.1)	0.55
Peripheral arterial disease	619 (9.2)	5 (0.1)	394 (9.9)	225 (8.2)	0.02
Chronic obstructive pulmonary disease	1,809 (26.9)	5 (0.1)	1,242 (31.3)	567 (20.6)	<0.001
Dementia	962 (14.3)	5 (0.1)	667 (16.8)	295 (10.7)	<0.001
Active neoplasia	939 (14.0)	7 (0.1)	570 (14.4)	369 (13.4)	0.28
Prior episodes of acute heart failure	4,061 (60.8)	47 (0.7)	2,414 (61.2)	1,647 (60.2)	0.42
Baseline status					
Barthel Index (points) (mean (SD))	77 (26)	830 (12.3)	75 (27)	80 (24)	<0.001
NYHA class III-IV	1,655 (26.2)	418 (6.2)	1,006 (26.7)	649 (26.5)	0.35
Left ventricular ejection fraction (%) (mean (SD))	51.5 (15.3)	3,003 (44.6)	52.4 (14.9)	50.4 (15.7)	<0.001
Chronic treatments at home					
Diuretics (any)	5,137 (78.6)	193 (2.9)	3,008 (78.0)	2,129 (79.5)	0.16
ACE inhibitor or ARB	3,676 (56.3)	193 (2.9)	2,151 (55.8)	1,525 (56.9)	0.35
Beta-blocker	2,672 (40.9)	196 (2.9)	1,508 (39.1)	1,154 (43.5)	<0.001
Mineralocorticoid-receptor antagonist	1,136 (17.4)	193 (2.9)	618 (16.0)	518 (19.3)	0.001
Digoxin	1,018 (15.6)	201 (3.0)	587 (15.2)	431 (16.1)	0.34
Vitals at ED during acute episode (mean (SD))					
SBP (mmHg)	139 (26)	101 (1.5)	139 (27)	139 (24)	0.33
Heart rate (bpm)	85 (21)	140 (2.1)	88 (22)	82 (18)	<0.001
Room air oxygen saturation (%)	91.9 (6.7)	182 (2.7)	91.2 (6.9)	92.9 (6.3)	<0.001
Results of blood tests at ED					
Haemoglobin (g/L) (mean (SD))	121 (20)	59 (0.9)	120 (20)	121 (19)	0.02
Leukocytes (cells/ μ L) (median (IQR))	8.4 (6.6-10.8)	69 (1.0)	9.2 (7.0-12.1)	7.8 (6.2-9.7)	<0.001
Glucose (mg/dL) (mean (SD))	149 (89)	123 (123)	155 (101)	140 (62)	<0.001
Creatinine (mg/dL) (mean (SD))	1.34 (0.80)	80 (1.2)	1.35 (0.78)	1.34 (0.82)	0.60
Sodium (mmol/L) (mean (SD))	138.0 (5.1)	128 (1.9)	137.7 (5.2)	138.3 (5.0)	<0.001
Potassium (mmol/L) (mean (SD))	4.42 (0.69)	423 (6.3)	4.42 (0.70)	4.41 (0.68)	0.61
Raised troponin (>99th percentile)	1,954 (55.9)	3,230 (48.0)	1,128 (55.8)	826 (56.0)	0.87
NT-proBNP (pg/mL) (median (IQR))	3,822 (1,830-8,432)	3,611 (53.7)	3,976 (1,942-8,630)	3,712 (1,667-8,186)	0.04

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; ED: emergency department; AHF: acute heart failure.

Bold p values denote statistical significance. NYHA: New York Heart Association; SBP: systolic blood pressure; SD: standard deviation; ED: emergency department; IQR: interquartile range

Figure 1: Patient inclusion flow chart

AHF: acute heart failure

Figure 2: Kaplan-Meier curves of events for primary (upper panel) and secondary (middle panels) outcomes comparing patients with an acute heart failure episode triggered by an infection and those with no trigger identified, as well as results of unadjusted and adjusted hazard ratios for the first respect to the second group of patients (lower panel).

	% patients with outcomes according to trigger (infection vs none identified)	Unadjusted HR for infection (95% CI)	Adjusted HR for infection (95% CI)
Primary outcome			
90-day all-cause mortality	11.9% vs 9.6%	1.11 (0.99-1.25)	0.91 (0.81-1.02)
Secondary outcomes (post-discharge)			
90-day all-cause mortality	5.4% vs 5.7%	0.97 (0.84-1.12)	0.83 (0.71-0.86)
90-day readmission due to AHF	25.6% vs 26.3%	0.95 (0.87-1.04)	0.92 (0.84-0.99)
90-day combined endpoint	27.8% vs 28.6%	0.97 (0.89-1.05)	0.92 (0.85-0.99)

Bold numbers in table denote statistical significance.

Figure 3: Time trend of hazard ratios for patients with an acute heart failure episode triggered by infection compared to patients with no trigger identified along the different time periods for primary and secondary outcomes.

Asterisks denote $p < 0.05$ for patients with infection compared to patients with no trigger.

Figure 4: Adjusted analysis of primary and secondary outcomes stratified by early antibiotic therapy and final disposition after emergency department care.

Bold p values denote statistical significance.

Supplemental Table 1: Dictionary of the variables included in the present study.

DEMOGRAPHICS	
Age	Age calculated as the difference in decimal years between the date of inclusion in the study and the date of birth.
Sex	Male/Female
MEDICAL HISTORY	
Hypertension	Indicate if the patient has arterial hypertension because this is shown under previous clinical history or the patient is receiving specific treatment.
Diabetes Mellitus	Indicate if the patient has diabetes mellitus because this is shown under previous clinical history or the patient is receiving specific treatment.
Ischaemic heart disease	Indicate if the patient has any form of ischaemic heart disease (SCAEST, SCACEST, unstable angina, stable angina, ACI, etc) because this is shown under previous clinical history or the patient is receiving specific treatment.
Heart valve disease	Indicate if the patient has any type of clinically significant heart valve disease according to an ultrasound or haemodynamic study reported in the previous clinical history.
Atrial fibrillation	Indicate if the previous history describes permanent or chronic atrial fibrillation or an ECG performed within the previous year shows atrial fibrillation and this continues to be present.
Chronic kidney disease	Indicate if the patient has chronic renal insufficiency or chronic kidney disease or if analyses over the previous year show creatinine values >2 mg/dL.
Cerebrovascular disease	Indicate if the patient has had a previous cerebrovascular accident or cerebrovascular disease because this is described in the clinical history or shown in CT or MR imaging studies within the previous year and reported as cerebrovascular disease.
Peripheral artery disease	Indicate if the patient has peripheral artery disease in either the lower extremities or carotid artery, and if the patient is receiving specific treatment, has undergone specific surgery (bypass of lower extremities, endarterectomy, etc.) or there is previous history of an ankle brachial index <0.90.
Dementia	Indicate if the patient has a previous clinical diagnosis of dementia performed by a doctor.
Active neoplasia	Indicate if the patient has an active neoplasm
Prior episode of heart failure	Indicate if the patient has heart failure, is receiving specific treatment or the clinical history reports previous episodes of AHF.
BASELINE STATUS	
Baseline Barthel index	Barthel index value of the patient at least 15 days prior to the date seen in the ED.
Baseline functional grade for dyspnoea according to the NYHA scale	Indicate the functional grade of basal dyspnoea (in the 15 days prior to the exacerbation episode) of the patient according to the NYHA scale.
Left ventricular ejection fraction	Indicate left ventricular ejection fraction determined by echocardiography during admission of current episode or, if not determined, the last one determined during the six previous months
CHRONIC TREATMENT AT HOME	
Diuretics	Receiving chronic treatment with diuretics, either loop-diuretics, thiazide diuretics or mineralocorticoid receptor antagonists
Angiotensin-converter enzyme (ACE) inhibitors or angiotensin-II receptor blocker	Receiving chronic treatment with ACE inhibitors or angiotensin-II receptor blocker
Beta-blocker	Receiving chronic treatment with beta-blocker
Mineralocorticoid-receptor antagonists	Receiving chronic treatment with aldosterone-receptor antagonists
Digoxin	Receiving chronic treatment with digoxin
VITAL SIGNS AT EMERGENCY DEPARTMENT ARRIVAL	
Systolic blood pressure	Systolic blood pressure (SBP) measured in mmHg of the patient on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care.
Heart rate	Central heart rate measured as beats per minute of the patient on arrival to the ED. V This value can be that obtained during triage or the first taken on initiating care .
Arterial oxygen saturation	Oxygen saturation expressed as percentage obtained by capillary pulsioxymetry on arrival to the ED. This value can be that obtained during triage or the first taken on initiating care.
BLOOD TESTS AT EMERGENCY DEPARTMENT ARRIVAL	
Glucose	In mg/dL
Creatinine	In mg/dL
Haemoglobin	In g/dL
Leukocytes	In cell/ μ L
Potassium	In mmol/L
Sodium	In mmol/L
Raised troponin	Indicate if troponin is above the 99th percent provided by the manufacturer

NT-proBNP	In pg/mL
TRIGGERING FACTORS OF THE CURRENT EPISODE OF ACUTE HEART FAILURE	
Infection	Active infection, of any system, considered to have a role in acute decompensation
Rapid atrial fibrillation	Mean heart rate >100 bpm, considered to have a role in acute decompensation
Anaemia	Haemoglobin <80 g/L, considered to have a role in acute decompensation
Hypertensive emergency	Systolic blood pressure >180 mmHg, considered to have a role in acute decompensation
Acute coronary syndrome	Symptoms starting before decompensation, and not developing after dyspnoea appearance
Dietetic/Therapeutic transgression	High water or sodium intake, omission to take drugs prescribed for heart failure treatment
Other	Describe specifically other adjudicated causes of decompensation not included in the previous episodes
Multifactorial	When some factors concur, but none is of sufficient magnitude to explain the decompensation by itself
None identified	When none of the previous factors can be selected