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ORIGINAL PAPER

The role of atrial fibrillation in the short-term outcomes of patients with acute heart failure

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Abstract

Aims To investigate whether the presence of atrial fibrillation (AF) is independently associated with adverse short-term outcomes in patients diagnosed with acute heart failure (AHF) in the emergency department (ED).

Methods We performed a secondary analysis of patients included in the EAHFE registries 4&5. Patients were divided by the presence of sinus rhythm (SR) or AF at ED arrival. The primary outcome was 30-day all-cause mortality. Secondary outcomes included the 30-day post-discharge combined endpoint of ED revisit or hospitalisation due to AHF and all-cause mortality. We recorded 54 independent variables that can affect outcomes. Cox regression was used to investigate adjusted significant associations between AF and outcomes. Analyses were repeated according to whether AF was previously known and whether AF was considered responsible for the AHF episode.

Results We analysed 6045 ED visits (mean age 80.4 years, 55.9% women), 3644 (60.3%) with AF. The cumulative 30-day mortality was 9.4%, and the adverse combined endpoint (ACE) was 25.9% (ED revisit with and without hospitalisation were 16.5 and 8.9% and death occurred in 4.7%). No differences were found in outcomes of AHF patients with SR and AF, and among the latter group, no differences were found depending on whether AF was considered responsible for the AHF episode. Patients with previously known AF had significantly lower 30-day mortality and higher post-discharge ACE rates, although these differences disappeared after adjustment for confounders HR 0.782, 95% CI 0.590–1.037, $p = 0.087$; and HR 1.131, 95% CI 0.924–1.385, $p = 0.234$).

Conclusion The coexistence of AF does not impact the short-term outcomes of patients diagnosed with AHF in the ED.

Keywords Atrial fibrillation · Acute heart failure · Emergency department · Outcome · Mortality · Revisit · Hospitalisation

Introduction

Acute heart failure (AHF) is a life-threatening condition associated with a 30-day all-cause mortality of approximately 10% and a re-hospitalisation rate (due to persistence or new AHF) of 20% [1, 2]. The emergency department (ED) plays a central role in the management of AHF, since about 90% of patients with this condition attend an ED to attend their symptoms [3]. In contrast with studies based only on hospitalised patients, ED registries can provide accurate information of the AHF population, since they include minor non-hospitalised decompensations. Depending on the country and healthcare system, the rate of non-hospitalised ED AHF patients is 16–36% [2, 4, 5]. Nonetheless, only three main registries have focused on the management of AHF in the ED [2, 6, 7], and they have shown that ED AHF patients are older than those with AHF included in hospitalised patient-based clinical trials and registries. Accordingly, some relevant aspects of the clinical profile of decompensated patients differ, and the number of concurrent comorbidities is usually higher [2].

Rodolfo Romero and Josep Mª Gaytan have equally contributed to this study and should both be considered as first author.

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Atrial fibrillation (AF) is one of the comorbidities frequently observed in AHF. A recent extensive review of 16 large registries has shown it is present in 24.4–53.1% of cases [2]. However, the impact of AF on outcomes in AHF patients and the necessity to control the heart rate is still not clear. Large AHF registries and trials comparing the prognostic impact of sinus rhythm (SR) with AF have shown that only SR patients may benefit from a reduction in heart rate [8]. In addition, AF may also be a precipitant for AHF in a patient who had been well compensated until AF caused decompensation, mainly due to tachyarrhythmia. A recent systematic review of 20 registries found that this situation could account for 5–38% of AHF cases [9]. In the largest analysis of the role of AF in the prognosis of patients with AHF, Arrigo et al. evaluated 15,828 patients with AHF hospitalised in European and Asian hospitals. They found that when AHF was precipitated by AF, there was a trend toward reduced mortality during the first weeks, which became similar to AHF without identified precipitants after this time period [10]. These studies indicate the need for further investigation into the impact of AF on the short-term outcomes of patients with AHF, especially from the wider perspective of patients diagnosed with AHF in the ED. Consequently, our hypothesis was that different short-term outcomes may be seen in ED AHF patients based on their electrocardiogram (ECG) at presentation (AF vs. SR), as well as depending on different aspects of AF presentation, especially if AF is considered responsible for the current AHF episode.

Patients and methods

Setting

We performed a secondary analysis of 7946 patients included in the EAHFE (*E*pidemiology of *A*cute *H*eart *F*ailure in *E*mergency Department) registries 4 and 5, with protocol being extensively reported elsewhere [11–13]. The criterion for a patient to be included in the EAHFE Registry is to be diagnosed with AHF in the ED based on the Framingham clinical diagnostic criteria [14]. The inclusion of patients is consecutive during the recruitment periods, and the only exclusion criterion is to have a concurrent diagnosis of ST-elevation myocardial infarction (STEMI). Phases 4 and 5 of patient recruitment took place from February 1 to March 31, 2014, and January 1 to February 29, 2016, respectively. Overall, 34 Spanish hospitals participated, representing 10% of the 339 Spanish public hospitals. Hospital participation in the registry was by convenience, but represents the full spectrum of Spanish healthcare centers attending AHF patients (university and community hospitals, as well as EDs with high-, medium-, and low-activity). The final adjudication of the AHF diagnosis is performed by the principal investigator of each centre based on review of medical charts and all complementary tests done during ED stay and hospitalisation. When available, every diagnosis was confirmed by natriuretic peptide determination or echocardiography following the European Society of Cardiology criteria [15]. However, patients with clinical diagnostic criteria, but without echocardiographic or natriuretic peptide confirmation, were included to obtain a cohort as close as possible to what is usually observed in emergency medicine practice. The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions.

Study design

AHF patients in the EAHFE Registries 4 and 5 were analysed to identify AF status. Patients were included if an ECG was obtained at the index ED visit, and 30-day mortality status was recorded. Patients with ECG rhythms other than SR or AF were excluded (i.e., patients with atrial flutter were not included in the AF group). In addition, we also excluded patients in SR but with a previous history of AF, because we wanted to avoid the potential confusion of including in the sinus group patients with paroxysmal AF but that were found in SR during the ED index episode. However, we used these patients (fount in SR but with previous history of AF) to run sensitivity analysis (see below, in the statistical analysis subheading). Patients were then divided according to SR or AF status at ED arrival. In addition, we also planned to run two additional analysis in the subset of patients in AF to test some factors that we thought they could influence outcomes; accordingly, AF patients with previously known AF were compared with AF patients with previously unknown AF, as well AF patients in whom AF was considered responsible for the current AHF episode were compared with patients in whom AF was not considered to be related with the AHF episode. In addition to ECG rhythm, 57 independent variables that could act as potential confounders were recorded. With respect to troponin, since there was not a common troponin assay in all centers, we considered as raised troponin those values above the 99th percentile of normality defined by the manufacturer, independently of the assay used.

Outcomes

The primary outcome was 30-day all-cause mortality. ED presentation was considered the index event. Secondary outcomes included the post-discharge (from ED or hospital) adverse combined endpoint (ACE) of 30-day ED revisit or hospitalisation due to AHF, or all-cause mortality, and the three ACE components individually. All endpoints were assessed by a phone call and review of primary care and

hospital medical records between 30 and 90 days after ED discharge.

Statistical analysis

Qualitative variables are expressed as frequency and percentage, and continuous variables as mean and standard deviation (SD), or if not normally distributed, as median and interquartile range (IQR). Comparisons were performed by means of the Chi-square test or the unpaired *T* test (or Mann–Whitney *U* test for non-normally distributed variables). Primary and secondary outcomes were assessed using the Kaplan–Meier survival tables and curves, and unadjusted comparisons between groups were performed using the log-rank test. We used the Cox-regression model to adjust survival by variables that were differently distributed between groups in the univariate analysis using the enter method to adjust hazard ratio estimation by the differences of our group populations. Prior to multivariate analysis, the multiple imputation methodology was used to produce 10 data sets replacing the missing values in the variables introduced in the Cox model. Differences between groups were expressed as unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). As sensitivity analysis, we repeated the adjusted estimations including those patients in current SR but with previous episodes of AF into the SR group; and then repeated the sensitivity analysis including them into the AF group. Statistical significance was accepted if the p value was <0.05 or if the 95% CI of the HR excluded the value 1. Since this was an exploratory study, a pre-hoc sample size calculation was not made. All calculations were made using SPSS software v.24 (IBM, New Castle, NY, USA).

Ethics

The EAHFE Registry followed the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and patients gave informed consent to participate and to be contacted for follow-up. The protocol was approved by the Ethical Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with reference numbers 166/13 and 160/15.

Results

Of the 7946 patients, 6045 (76.1%) were included in this study (Fig. 1). The mean (SD) age of patients included in the present analysis was 80.4 (8.5) years, 55.9% were women, and 45.1% had de novo AHF. Comorbidities and chronic treatments at home were frequent (Table 1); most had hypertension and one-third had a reduced ejection fraction (reduced 18.8%, mid-range 13.4%, preserved 67.8%). Echocardiography data was available in 4062 patients (67.2%), NT-proBNP in 2787 (46.1%) and BNP in 426 (7.0%). Only 938 out of the 6045 patients (15.5%) did not have any of these tests performed. Table 1 contains the results for NT-proBNP and left ventricular ejection fraction, which was specified in 3472 out of the 4062 patients with echocardiography. The majority received outpatient diuretics and renin angiotensin system (RAS) inhibitors, although less than half were treated with beta-blockers. Upon arrival to the ED, 43.4% had NYHA class IV, most had an elevated troponin level, and the mean NT-proBNP was 3.748 pg/mL. In the ED, most patients received diuretics and oxygen, but nitroglycerin and morphine were infrequently used (11.9% and 6%, respectively). Treatment at discharge comprised diuretics in around three quarters of the patients, with RAS inhibitors and beta-blockers in about half. Overall, 75.8% of patients were hospitalised, and median length of hospitalisation was 7 days (IQR 4–11 days).

Overall, 3644 patients (60.3%) had AF in the ED, and 2401 (39.7%) were in SR. AF patients differed from those in SR in 41 out of the 57 variables (Table 1). SR patients more frequently had diabetes, ischaemic heart disease, chronic kidney disease, peripheral artery disease, cancer and a reduced ejection fraction, whereas patients in AF were older and had a higher frequency of heart valve disease, cerebrovascular disease and previous AHF episodes. Overall, patients with AF were receiving more chronic treatment compared to those in SR, mainly due to the use of diuretics, beta-blockers, amiodarone, digoxin and vitamin K antagonists. Upon arrival to the ED, patients with AF had a higher heart rate and lower blood pressure, and were more likely to receive beta-blockers, digoxin and amiodarone. AF patients were more likely to be discharged on beta-blockers, digoxin, amiodarone, vitamin K antagonists and direct oral anticoagulants, and less likely to receive RAS inhibitors, calcium antagonists and antiplatelet agents.

The cumulative 30-day mortality for the whole cohort was 9.4% (568 patients). In-hospital mortality was 7.0% (423 patients) and median time to die was 6 days (IQR: 3–13 days). For those patients discharged alive after the index episode (i.e., after exclusion of patients experiencing in-hospital death), the 30-day post-discharge ACE was 25.9% (1565 patients). Individually, the 30-day post-discharge ED revisit without hospitalisation due to AHF was 8.0% (438 patients), the 30-day post-discharge hospitalisation due to AHF was 15.4% (837 patients), and the 30-day post-discharge all-cause death was 4.9% (272 patients). On comparing AF and SR patients, there were no differences in 30-day all-cause mortality or post-discharge ACE (Fig. 2). After adjustment for the 38 variables differently distributed between the AF and SR groups, there were no differences between groups for 30-day all-cause mortality or 30-day post-discharge ACE

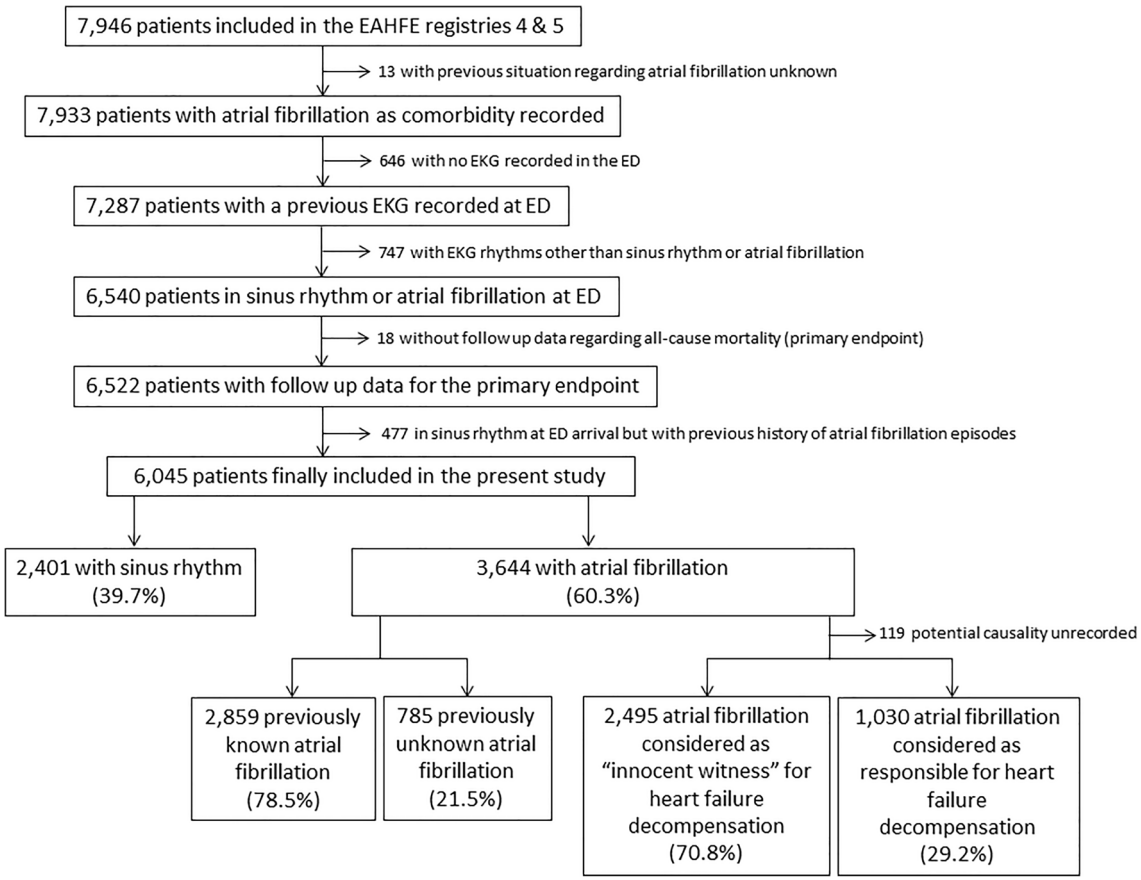

Fig. 1 Flow chart of patient inclusion in the present study

(all p > 0.05) (Table 2). Analysis of individual unadjusted or adjusted secondary endpoints found no differences between AHF patients in SR and patients in AF (Table 2).

The 3644 AHF patients with AF were divided into those with known previous AF [n = 2859 (78.5%)] and unknown previous AF [*n* = 785 (21.5%)]. The unadjusted 30-day all-cause mortality was lower in patients with known AF than in those with unknown previous AF (HR 0.786, 95% CI 0.618–0.999, *p* = 0.049), while the unadjusted 30-day post-discharge combined endpoint was higher (HR 1.221, 1.023–1.458, p = 0.027) (Fig. 2; Table 2). No differences were found in the individual secondary endpoints. After adjustment for the 33 variables distributed differently between previously known and unknown AF groups (Table 3), no differences remained statistically significant (Table 2). On the other hand, when the 3644 AHF patients with AF were divided into 1030 cases (29.2%) in whom AF was considered responsible for the current episode of AHF and 2495 cases (70.8%) in whom AF was not considered responsible for the AHF episode ("innocent witness"), there were no differences in any outcomes; nor were there outcome differences after adjustment for the 37 variables distributed differently between groups (Tables 2, 3).

Discussion

Heart failure and AF are two cardiovascular epidemics, and these two entities frequently coexist in a single patient [16]. Many studies have discussed the impact that each has on the other in regard to outcomes, with no general agreement to date [16–23]. In the present study, we evaluated the short-term outcomes of consecutive heart failure patients attended in the ED because of acute decompensation, with around 60% having concurrent AF. Remarkably, our cohort was formed by more than two-third of patients with preserved left ventricular ejection fraction, a proportion clearly higher than that observed in the landmark AHF trials, that usually are below one-third [20, 21]. The fact that our patients were recruited in the ED has clearly influenced in this difference, as our patients are older and with less prevalence of ischemic cardiomyopathy past history. Nonetheless, we believe that ED is a setting that provides a better approach to the universe of patients with AHF than the hospitalisation setting, where randomized trials are usually run. Taking into account all these circumstances, we concluded that the coexistence of AF does not have an impact on the short-term outcomes of patients diagnosed with AHF in the ED, irrespectively

Table 1 Clinical characteristics of the 6045 patients with acute heart failure included in the study, and comparison depending on whether they presented sinus rhythm or atrial fibrillation at emergency department arrival

	Total *N* = 6045 *n* (%)	Missing values (%)	Sinus rhythm *N* = 2401 *n* (%)	Atrial fibrillation *N* = 3644 *N* (*n*)	*p* value
Epidemiological data					
Age (years) [mean (SD)]	80.4 (10.3)	5 (0.1)	78.4 (11.7)	81.8 (8.9)	< **0.001**
Female sex	3364 (55.9)	28 (0.5)	1308 (54.7)	2056 (56.7)	0.127
Comorbidities					
Hypertension	5076 (84.0)	2 (0.0)	2001 (83.4)	3075 (84.4)	0.284
Diabetes mellitus	2505 (41.4)	0 (0)	1123 (46.8)	1382 (37.9)	< **0.001**
Ischaemic heart disease	1696 (28.1)	1 (0.0)	798 (33.3)	898 (24.6)	< **0.001**
Chronic kidney disease (creatinine > 2 mg/dL)	1563 (25.9)	1 (0.0)	669 (27.9)	894 (24.5)	**0.004**
Cerebrovascular disease	757 (12.5)	2 (0.0)	265 (11.0)	492 (13.5)	**0.005**
Heart valve disease	1525 (25.2)	2 (0.0)	474 (19.8)	1051 (28.8)	< **0.001**
Peripheral artery disease	559 (9.3)	3 (0.0)	260 (10.8)	299 (8.2)	**0.001**
Chronic obstructive pulmonary disease	1380 (22.8)	2 (0.0)	536 (22.3)	844 (23.2)	0.450
Dementia	839 (13.9)	3 (0.0)	311 (13.0)	528 (14.5)	0.090
Cancer	847 (14.0)	5 (0.1)	387 (16.1)	460 (12.6)	< **0.001**
Previous episodes of acute heart failure	3312 (54.9)	16 (0.3)	1152 (48.1)	2160 (59.4)	< **0.001**
Reduced left ventricular ejection fraction (< 50%)	1115 (32.2)	2583 (42.7)	500 (39.3)	615 (28.1)	< **0.001**
Chronic treatments at home					
Diuretics (any)	4363 (75.4)	258 (4.3)	1558 (68.6)	2805 (79.8)	< **0.001**
Renin–angiotensin system inhibitors	3267 (56.5)	258 (4.3)	1283 (56.5)	1984 (56.4)	0.984
Mineralocorticoid-receptor antagonists	945 (16.3)	258 (4.3)	307 (13.5)	638 (18.2)	< **0.001**
Beta-blockers	2614 (45.2)	261 (4.3)	911 (40.1)	1793 (48.5)	< **0.001**
Calcium antagonists	1573 (27.2)	259 (4.3)	638 (28.1)	935 (26.6)	0.213
Amiodarone	221 (3.8)	259 (4.3)	56 (2.5)	165 (4.7)	< **0.001**
Digoxin	805 (13.9)	264 (4.4)	36 (1.6)	769 (21.9)	< **0.001**
Antivitamin K	2115 (36.6)	259 (4.3)	155 (6.8)	1960 (55.8)	< **0.001**
Direct-action anticoagulants	343 (5.9)	258 (4.3)	32 (1.4)	311 (8.8)	< **0.001**
Antiaggregants	2053 (35.5)	259 (4.3)	1176 (51.8)	877 (25.0)	< **0.001**
Clinical status at ED arrival					
Systolic blood pressure (mmHg) [mean (SD)]	141 (27)	71 (1.2)	145 (29)	138 (25)	< **0.001**
Heart rate (bpm) [mean (SD)]	90 (24)	111 (81.8)	85 (18)	93 (26)	< **0.001**
Room-air pulsioxymetry (%) [mean (SD)]	92.4 (6.6)	178 (2.9)	91.9 (6.9)	92.7 (6.3)	< **0.001**
NYHA functional class IV, *n* (%)	2544 (43.4)	189 (3.1)	1014 (43.7)	1530 (43.3)	0.795
Barthel index (points) [mean (SD)]	66 (29)	1555 (25.7)	67 (29)	66 (29)	0.313
Laboratory data					
Haemoglobin (g/L) [mean (SD)]	120 (21)	51 (0.8)	119 (22)	121 (21)	**0.001**
Glucose (mg/dl) [mean (SD)]	148 (84)	98 (1.6)	157 (102)	142 (68)	< **0.001**
Creatinine (mg/dl) [mean (SD)]	1.33 (0.84)	68 (1.1)	1.39 (1.00)	1.28 (0.72)	< **0.001**
Sodium (mEq/L) [mean (SD)]	138.4 (4.9)	152 (2.5)	138.5 (5.0)	138.3 (4.8)	0.180
Potassium (mEq/L) [mean (SD)]	4.41 (0.70)	398 (6.6)	4.45 (0.72)	4.38 (0.69)	< **0.001**
NT-proBNP (pg/mL) (median, IQR)	3748 (5966)	3258 (53.9)	3450 (7603)	3952 (5434)	**0.003**
Elevated troponin	1913 (57.8)	2733 (45.2)	815 (61.0)	1098 (55.6)	**0.002**
Treatment and management at ED					
Oxygen	4240 (70.7)	45 (0.7)	1658 (69.7)	1582 (71,3)	0.167
Non-invasive ventilation	404 (6.7)	44 (0.7)	214 (9.0)	190 (5.2)	< **0.001**
Mechanical ventilation	244 (4.1)	43 (0.7)	111 (4.7)	133 (3.7)	0.058
Morphine	360 (6.0)	43 (0.7)	184 (7.7)	176 (4.9)	< **0.001**
Diuretics (IV)	5006 (83.4)	46 (0.8)	1971 (82.8)	3035 (83.9)	0.285

Table 1 (continued)

	Total $N=6045$ n (%)	Missing values (%)	Sinus rhythm $N=2401$ n (%)	Atrial fibrillation $N=3644$ N (n)	p value
Nitroglycerin (IV)	713 (11.9)	43 (0.7)	362 (15.2)	351 (9.7)	**< 0.001**
Inotropic or vasopressor treatment	80 (1.3)	47 (0.8)	37 (1.6)	43 (1.2)	0.225
Beta-blockers	932 (15.5)	44 (0.7)	280 (11.8)	652 (18.0)	**< 0.001**
Digoxin	809 (13.5)	43 (0.7)	31 (1.3)	778 (21.5)	**< 0.001**
Amiodarone	190 (3.2)	43 (0.7)	30 (1.3)	160 (4.4)	**< 0.001**
Hospitalised	4583 (75.8)	1 (0.0)	1799 (74.9)	2784 (76.4)	0.185
Treatment at discharge					
Diuretics (any)	4330 (77.7)	475 (7.9)	1701 (76.7)	2629 (78.4)	0.126
Renin–angiotensin system inhibitors	2731 (49.0)	476 (7.9)	1159 (52.3)	1572 (46.9)	**< 0.001**
Mineralocorticoid-receptor antagonists	1091 (19.6)	475 (7.9)	419 (18.9)	672 (20.0)	0.287
Beta-blockers	2425 (43,6)	482 (8.0)	882 (39,8)	1543 (46.1)	**< 0.001**
Calcium antagonists	1150 (20.8)	475 (7.9)	503 (22.7)	656 (19.6)	**0.005**
Amiodarone	215 (3.9)	478 (7.9)	66 (3.0)	149 (4.4)	**0.005**
Digoxin	759 (13.6)	476 (7.9)	34 (1.5)	725 (21.6)	**< 0.001**
Antivitamin K	1842 (33.1)	478 (7.9)	170 (7.7)	1672 (49.9)	**< 0.001**
Direct-action anticoagulants	388 (7.0)	477 (7.9)	36 (1.6)	352 (10.5)	**< 0.001**
Antiaggregants	1705 (30.6)	476 (7.9)	2217(45.7)	691 (20.6)	**< 0.001**

Bold numbers in the p value columns indicate statistical significance

ED emergency department

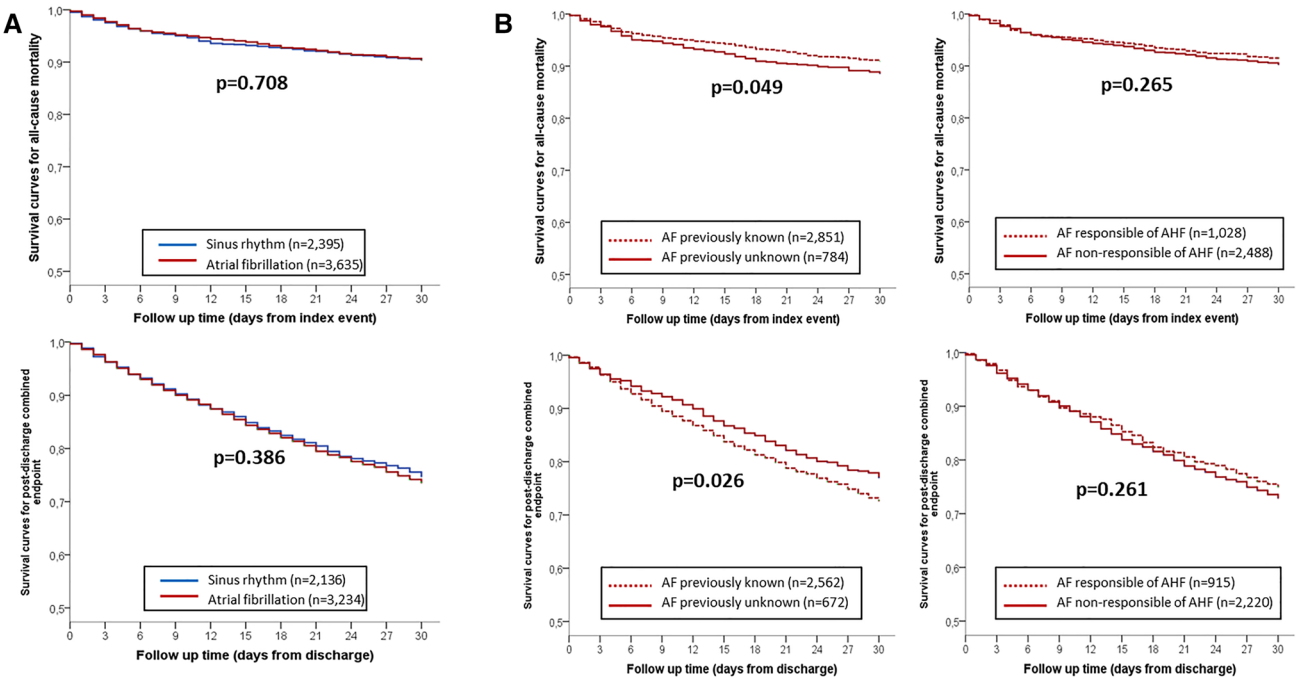

Fig. 2 Kaplan–Meier survival curves for all-cause 30-day mortality (primary endpoint; up) and for 30-day post-discharge combined endpoint (ED revisit or hospitalisation due)

Table 2 Unadjusted and adjusted analyses for primary and secondary endpoints according to whether patients presented sinus rhythm or atrial fibrillation at emergency department arrival, whether atrial fibrillation was previously known or unknown, and whether atrial fibrillation was considered responsible or not responsible for the decompensation

	Unadjusted analysis		Adjusted analysis		Adjusted analysis (sensitivity analysis 1)[a]		Adjusted analysis (sensitivity analysis 2)[a]	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
For patients in AF with respect to sinus rhythm								
Primary endpoint								
30-day all-cause mortality	1.033 (0.872–1.222)	0.708	1.048 (0.833–1.319)	0.686	0.972 (0.800-1.182)	0.779	1.054 (0.856–1.298)	0.622
Secondary endpoints								
30-day PD combined endpoint (ED revisit/hospitalisation/death)	1.049 (0.941–1.171)	0.388	0.936 (0.809–1.084)	0.376	0.945 (0.830–1.075)	0.386	0.992 (0.863–1.140)	0.905
30-day PD ED revisit (without hospitalisation) due to AHF	1.006 (0.829–1.220)	0.954	1.004 (0.773–1.304)	0.976	1.012 (0.803–1.274)	0.922	0.988 (0.770–1.267)	0.923
30-day PD hospitalisation due to AHF	1.064 (0.925–1.224)	0.385	0.879 (0.728–1.062)	0.181	0.895 (0.758–1.056)	0.189	0.980 (0.819–1.172)	0.821
30-day PD all-cause mortality	1.025 (0.758–1.388)	0.871	0.916 (0.663–1.267)	0.597	0.902 (0.668–1.218)	0.501	1.046 (0.861–1.271)	0.649
For AF patients with previously known AF compared to previously unknown AF								
Primary endpoint								
30-day all-cause mortality	**0.786 (0.618–0.999)**	**0.049**	0.782 (0.590–1.037)	0.087	–	–	0.823 (0.627–1.080)	0.160
Secondary endpoints								
30-day PD combined endpoint (ED revisit/hospitalisation/death)	**1.221 (1.023–1.458)**	**0.027**	1.131 (0.924–1.385)	0.234	–	–	1.199 (0.983–1.462)	0.073
30-day PD ED revisit (without hospitalisation) due to AHF	1.166 (0.852–1.595)	0.338	1.184 (0.827–1.696)	0.357	–	–	1.201 (0.844–1.711)	0.309
30-day PD hospitalisation due to AHF	1.175 (0.940–1.470)	0.157	1.023 (0.792–1.322)	0.862	–	–	1.110 (0.863–1.426)	0.416
30-day PD all-cause mortality	1.506 (0.885–2.561)	0.131	1.249 (0.787–1.981)	0.346	–	–	1.252 (0.973–1.611)	0.081
For AF responsible for decompensation compared to AF not responsible								
Primary endpoint								
30-day all-cause mortality	0.870 (0.681–1.112)	0.266	0.947 (0.696–1.288)	0.728	–	–	0.865 (0.643–1.164)	0.339
Secondary endpoints								
30-day PD combined endpoint (ED revisit/hospitalisation/death)	0.916 (0.785–1.069)	0.264	0.997 (0.823–1.207)	0.974	–	–	0.929 (0.768-1124)	0.447
30-day PD ED revisit (without hospitalisation) due to AHF	1.085 (0.829–1.420)	0.552	1.143 (0.815–1.603)	0.438	–	–	1.063 (0.758–1.490)	0.724
30-day PD hospitalisation due to AHF	0.891 (0.732–1.087)	0.256	0.969 (0.758–1.238)	0.802	–	–	0.923 (0.725–1.177)	0.520
30-day PD all-cause mortality	0.644 (0.402–1.031)	0.067	0.664 (0.420–1.049)	0.079	–	–	0.802 (0.611–1.053)	0.112

Bold numbers in the *p* value columns indicate statistical significance

AF atrial fibrillation, *ED* emergency department, *AHF* acute heart failure, *PD* post-discharge

[a]Sensitivity analysis consisted in including in the sinus rhythm group (sensitivity analysis 1) and in the atrial fibrillation group (sensitivity analysis 2) those patients that were in sinus rhythm at emergency department arrival but had a previous history of atrial fibrillation

or whether AF is or is not previously known, or if AF is or is not considered the precipitant of the AHF episode. We believe that the fact that these negative findings have been found by analyzing a large sample of patients makes unlikely the possibility of committing a type II error.

With respect to mortality, in 2002 Van den Berg et al. published a systematic review of the impact of AF on the survival of patients with chronic heart failure. They found six studies, including nearly 10,000 patients, in which mortality was assessed as a primary endpoint. They reported that, despite methodological differences among studies, AF was associated with a consistent increase in mortality in patients with mild-to-moderate (but not severe) forms of chronic heart failure [22]. As this finding was replicated in further studies, some authors agreed that AF could by itself actively cause progression of disease in patients with non-advanced stages of heart failure [18, 23]. Miyasaka et al. also found that in patients with AF who developed heart failure, there were similar mortality rates after 6 years of follow-up [24]. Alternatively, Smit et al. demonstrated that when AF appears first or concomitantly in the clinical course of patients with heart failure, these patients have better outcomes (mortality or cardiovascular admission at 18 months) than patients in whom AF appears at some point after the diagnosis of heart failure [25]. Importantly, all these studies evaluated the long-term prognosis of chronic heart failure patients; therefore, the effect of AF during acute decompensation was not assessed. In the present study, we noted a 30-day mortality of around 10% following such decompensations, a figure similar to that reported by others [23, 26], and that the risk of death after an episode of AHF was similar in patients with AF and SR. In our findings, the role of treatments on outcomes is difficult to delineate. For example, it is known that beta-blockers reduce mortality both in SR and in AF, and prevalence of this kind of drug (either as current or at discharge treatment) was different among groups [27]. Similarly, effect of tachycardia can differ between groups; while in patients with heart failure and reduced ejection fraction, higher heart rates are associated with increased mortality in SR, only heart rates over 100 bpm negatively influence in prognosis in patients in AF [27].

An additional remarkable finding of our study was that AF did not have an impact on the combined endpoint (ED revisit, hospitalisation or death), which was measured 30 days after patient discharge in patients with an acute decompensation. We failed to identify any previous study with a design similar to the present one with which to compare our results. The closest analysis to ours was reported by Abualnaja et al. [27], who investigated short-term outcomes (dyspnoea improvement and clinical 30-day mortality, readmission and composite endpoint) in 7007 patients in the ASCEND-HF trial. These authors reported that current or a history of AF is associated with less dyspnoea improvement and a higher morbidity and mortality at 30 days, with an adjusted odds ratio (OR) for a 30-day composite endpoint of 1.19 (1.02–1.38) for patients with AF. However, two main differences with the present study design should be noted: they did not include consecutive patients, and all the patients included were hospitalised. Therefore, these two facts could have biased the study by Abualnaja et al. towards patients with more severe episodes of AHF or AF, while our study probably better represents the whole universe of patients with AHF, since the exclusion criteria were minimal (only patients with AHF and concurrent STEMI).

Interestingly, in the subgroup of patients with AF, we found no differences in outcomes when these patients were compared according to known or unknown AF status, or if the AF was considered responsible for the AHF decompensation. In a previous study by our group, it was found that patients in whom AF was considered to be the precipitant of the decompensation showed a decreased risk for ED rehospitalisation and death in the subsequent 90 days (OR 0.67, 0.54–0.84; and OR 0.59, 0.32–1.09, respectively) [28]. A similar finding was reported by Arrigo et al. (HR 0.56, 0.42–0.76, for 90-day mortality), who suggested that the "beneficial effect" of AF is limited to the first 3 weeks following decompensation, with the presence of AF having a neutral effect until day 90 thereafter. However, in both studies, the comparator was patients without an identified precipitant factor, a group that also included a mixture of patients in SR and AF.

Our study has limitations. First, this was a secondary analysis without predefined hypothesis, and the results should only be considered as hypothesis-generating. In addition, groups´ population differed in many aspects, and we had to adjust outcomes for all these differences which makes our results weaker that if they were achieved in a more homogenous population. Second, we did not record if the strategy of AF treatment was rhythm or rate control in the ED or during follow-up. Third, the rhythm at discharge, from ED or hospital, and at the end of follow-up was not recorded. Fourth, we only collected the drugs but not doses administered, and therefore, we cannot comment on the appropriate use or how this would affect outcomes. In addition, some specific drugs used for AF treatment were not recorded. Fifth, interventions for rhythm or rate control in the prehospital setting before patient arrival to the ED were also not recorded, and there is increasing evidence that this may have an impact on short-term outcomes [29, 30]. Sixth, as there was no pre-hoc sample size calculation, it is not possible to exclude a beta-error in some estimation. Seventh, as some patients were admitted and others discharged during the AHF episode, the effect of hospitalisation was not controlled. We addressed this by defining post-discharge outcomes (and not after ED consultation), but cannot exclude the potential of a residual effect. Despite

Table 3 Clinical characteristics of patients with atrial fibrillation included in the study and comparison depending on whether the atrial fibrillation was previously known or unknown and whether the atrial fibrillation was considered responsible or not responsible for the decompensation

	Known AF *N* = 2859 *n* (%)	Unknown AF *N* = 785 *n* (%)	*p* value	AF responsible *N* = 1030 *n* (%)	AF not responsible *N* = 2495 *N* (*n*)	*p* value
Epidemiological data						
Age (years) [mean (SD)]	81.9 (8.5)	81.1 (10.4)	**0.016**	80.4 (10.2)	82.3 (8.3)	< **0.001**
Female sex	1627 (57.2)	429 (54.9)	0.240	640 (62.5)	1349 (54.3)	< **0.001**
Comorbidities						
Hypertension	2453 (85.8)	622 (79.2)	< **0.001**	825 (80.1)	2149 (86.1)	< **0.001**
Diabetes mellitus	1110 (38.8)	272 (34.9)	**0.033**	350 (34.0)	991 (39.7)	**0.001**
Ischaemic heart disease	704 (24.6)	194 (24.7)	0.959	192 (18.6)	678 (27.2)	< **0.001**
Chronic kidney disease (creatinine > 2 mg/dL)	761 (26.6)	133 (16.9)	< **0.001**	166 (16.1)	704 (28.2)	< **0.001**
Cerebrovascular disease	418 (14.6)	74 (9.4)	< **0.001**	105 (10.2)	369 (14.8)	< **0.001**
Heart valve disease	909 (31.8)	142 (18.1)	< **0.001**	235 (22.8)	787 (31.5)	< **0.001**
Peripheral artery disease	251 (8.8)	48 (6.1)	**0.016**	68 (6.6)	223 (8.9)	**0.023**
Chronic obstructive pulmonary disease	684 (23.9)	160 (20.4)	**0.037**	187 (18.2)	635 (25.5)	< **0.001**
Dementia	400 (14.0)	128 (16.3)	0.104	149 (14.5)	369 (14.8)	0.798
Cancer	364 (12.7)	96 (12.2)	0.709	125 (12.2)	322 (12.9)	0.540
Previous episodes of acute heart failure	1887 (66.1)	273 (34.9)	< **0.001**	443 (43.3)	1659 (66.5)	< **0.001**
Reduced left ventricular ejection fraction (< 50%)	505 (27.4)	110 (31.7)	0.102	147 (27.6)	442 (27.7)	0.959
Chronic treatments at home						
Diuretics (any)	2308 (83.4)	497 (66.5)	< **0.001**	655 (66.2)	2051 (85.2)	< **0.001**
Renin–angiotensin system inhibitors	1984 (56.4)	400 (53.5)	0.065	548 (55.4)	1381 (57.4)	0.274
Mineralocorticoid-receptor antagonists	541 (19.5)	97 (13.0)	< **0.001**	107 (10.8)	505 (21.0)	< **0.001**
Beta-blockers	1442 (52.2)	261 (34.9)	< **0.001**	458 (46.3)	1187 (49.4)	0.099
Calcium antagonists	747 (27.0)	188 (25.1)	0.306	238 (24.1)	662 (27.5)	**0.039**
Amiodarone	726 (26.3)	43 (5.7)	< **0.001**	39 (3.9)	120 (5.0)	0.188
Digoxin	141 (5.1)	24 (3.2)	**0.031**	130 (13.1)	606 (25.2)	< **0.001**
Antivitamin K	1800 (65.1)	160 (21.4)	< **0.001**	400 (40.4)	1488 (61.8)	< **0.001**
Direct-action anticoagulants	272 (9.8)	39 (5.2)	< **0.001**	79 (8.0)	221 (9.2)	0.261
Antiaggregants	607 (21.9)	270 (36.1)	< **0.001**	279 (28.2)	566 (23.5)	**0.004**
Clinical status at ED arrival						
Systolic blood pressure (mmHg) [mean (SD)]	138 (25)	137 (26)	0.215	138 (25)	139 (26)	0.323
Heart rate (bpm) [mean (SD)]	90 (25)	102 (30)	< **0.001**	114 (27)	84 (21)	< **0.001**
Room-air pulsioxymetry (%) [mean (SD)]	92.5 (6.5)	93.1 (5.4)	**0.017**	93.3 (5.8)	92.3 (6.5)	< **0.001**
NYHA Functional class > II, *n* (%)	1210 (43.6)	320 (42.3)	0.540	390 (38.8)	1090 (44.9)	**0.001**
Barthel index (points) [mean (SD)]	66 (29)	68 (30)	0.133	70 (29)	65 (29)	< **0.001**
Laboratory data						
Haemoglobin (g/L) [mean (SD)]	120 (21)	123 (21)	< **0.001**	127 (20)	119 (21)	< **0.001**
Glucose (mg/dl) [mean (SD)]	142 (69)	144 (65)	0.463	146 (67)	141 (68)	0.093
Creatinine (mg/dl) [mean (SD)]	1.29 (0.70)	1.26 (0.78)	0.273	1.20 (0.72)	1.31 (0.71)	< **0.001**
Sodium (mEq/L) [mean (SD)]	138.2 (4.8)	138.7 (4.9)	**0.006**	138.8 (4.8)	138.1 (4.8)	< **0.001**
Potassium (mEq/L) [mean (SD)]	4.38 (0.71)	4.38 (0.64)	0.926	4.37 (0.61)	4.38 (0.73)	0.630
NT-proBNP (pg/mL) (median, IQR)	3892 (5341)	4004 (5928)	0.367	3897 (5166)	3971 (5505)	0.821
Elevated troponin	832 (55.2)	266 (56.7)	0.576	329 (50.9)	726 (57.7)	**0.005**
Treatment and management at ED						
Oxygen	2018 (71.1)	564 (72.0)	0.622	694 (67.6)	1810 (73.1)	**0.001**
Non-invasive ventilation	138 (4.9)	52 (6.6)	**0.048**	68 (6.6)	115 (4.6)	**0.016**
Mechanical ventilation	102 (3.6)	31 (4.0)	0.631	34 (3.3)	97 (3.9)	0.394
Morphine	129 (4.5)	47 (6.0)	0.093	65 (6.3)	104 (4.2)	**0.007**
Diuretics (IV)	2373 (83.7)	662 (84.5)	0.557	853 (83.1)	2078 (83.9)	0.566

Table 3 (continued)

	Known AF $N=2859$ n (%)	Unknown AF $N=785$ n (%)	p value	AF responsible $N=1030$ n (%)	AF not responsible $N=2495$ N (n)	p value
Nitroglycerin (IV)	271 (9.5)	80 (10.2)	0.576	104 (10.1)	232 (9.4)	0.479
Inotropic or vasopressor treatment	30 (1.1)	13 (1.7)	0.168	14 (1.4)	28 (1.1)	0.563
Beta-blockers	505 (17.8)	147 (18.8)	**< 0.001**	286 (27.9)	343 (13.8)	**< 0.001**
Digoxin	538 (19.0)	240 (30.7)	**< 0.001**	470 (45.8)	294 (11.9)	**< 0.001**
Amiodarone	99 (3.5)	61 (7.8)	**< 0.001**	93 (9.1)	65 (2.6)	**< 0.001**
Hospitalised	2146 (75.1)	638 (81.3)	**< 0.001**	787 (76.4)	1912 (76.7)	0.870
Chronic treatments at home						
Diuretics (any)	2103 (79.7)	526 (73.9)	**0.001**	709 (74.1)	1841 (80.2)	**< 0.001**
Renin–angiotensin system inhibitors	1243 (47.1)	329 (46.3)	0.701	452 (47.3)	1080 (47.0)	0.900
Mineralocorticoid-receptor antagonists	549 (17.3)	549 (20.8)	**0.037**	146 (15.2)	502 (21.9)	**< 0.001**
Beta-blockers	1203 (45.6)	340 (47.9)	0.286	516 (54.1)	981 (42.8)	**< 0.001**
Calcium antagonists	523 (20.6)	113 (15.9)	**0.005**	163 (17.0)	468 (20.4)	**0.028**
Amiodarone	107 (4.1)	42 (5.9)	**0.034**	222 (23.1)	483 (21.0)	0.173
Digoxin	605 (23.0)	118 (16.6)	**< 0.001**	63 (6.6)	82 (3.6)	**< 0.001**
Antivitamin K	1414 (53.6)	258 (36.2)	**< 0.001**	442 (46.2)	1182 (51.5)	**0.006**
Direct-action anticoagulants	262 (9.9)	90 (12.6)	**0.036**	129 (13.5)	213 (9.3)	**< 0.001**
Antiaggregants	486 (18.4)	205 (28.8)	**< 0.001**	204 (21.3)	466 (20.3)	0.512

Bold numbers in the p value columns indicate statistical significance

ED emergency department

all these limitations, we believe that our results, which were identified in a large sample of representative ED patients with AHF, strongly suggest that the coexistence of AF, its known/unknown status and the physician's impression of AF contribution to heart failure decompensation have a minimal impact on short-term outcomes.

Conclusion

The coexistence of AF does not impact the short-term outcomes of patients diagnosed with AHF in the ED. However, our conclusion has to be cautiously interpreted considering all the previously commented limitations that this study has, and it will have to wait to be confirmed by further prospectively designed studies.

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Compliance with ethical standards

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