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Original Article

Digoxin and prognosis of heart failure in older patients with preserved ejection fraction: Importance of heart rate. Results from an observational and multicenter study

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ABSTRACT

Background: The value of digoxin in heart failure (HF) remains controversial, particularly in patients with preserved ejection fraction (HFpEF). This study evaluated the 1-year risk of events after digoxin treatment for acute heart failure (AHF) in patients > 70 years old with HFpEF.

Methods: 1833 patients were included in this analysis (mean age, 82 years). The main endpoints were all-cause death and the composite of death and/or HF re-admission within 1 year. Cox regression analysis was used to evaluate the association between digoxin treatment and prognosis.

Results: 401 patients received digoxin treatment; of these, 86% had atrial fibrillation. The mean baseline heart rate was 86 ± 22 bpm. At the 1-year follow-up, 375 patients (20.5%) died and 684 (37.3%) presented composite endpoints. Patients treated with digoxin showed higher rates of death (3.21 vs. 2.44 per 10 person-years, $p = .019$) and composite endpoint (6.72 vs. 5.18 per 10 person-years, $p = .003$). After multivariate adjustment, digoxin treatment remained associated with increased risks of death (HR = 1.46, 95% CI: 1.16–1.85, $p = .001$) and the composite endpoint (HR = 1.35, 95% CI: 1.13–1.61, p = .001). A distinctive prognostic effect of digoxin was found across the heart rate continuum; the risks for both endpoints were higher at lower heart rates and neutral at higher heart rates (p of the interactions = 0.007 and 0.03, respectively).

Conclusions: In older patients with HFpEF discharged after AHF, digoxin treatment was associated with increased mortality and/or re-admission, particularly in patients with lower heart rates.

Abbreviations: Acute heart failure, AHF; Angiotensin converting enzyme, ACE; Angiotensin receptor blockers, ARBs; Beat per minute, bpm; Ejection fraction, EF; Fractional polynomials, FP; The estimated glomerular filtration rate, based on the Modification of Diet in Renal Disease, eGFR-MDRD; Hazard ratios, HR; Heart failure, HF; Heart failure preserved ejection fraction, HFpEF; Heart failure reduced ejection fraction, HFrEF; Hemoglobin, Hb; Sinus rhythm, SR; Standard deviation, SD; Systolic blood pressure, SBP

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1. Introduction

Digoxin is widely used in managing patients with heart failure (HF) [1], although its use continues to generate intense controversy [2–7]. Current guidelines recommend digoxin use in patients with HF with reduced ejection fraction (HFrEF) and that are in sinus rhythm (SR) with a IIb level recommendation and a B grade of evidence [8]. Digoxin is also recommended for the control of heart rate in patients with atrial fibrillation [9]. The DIG study, the largest randomized trial in this field, and the only one to date, showed that digoxin had a neutral effect on mortality, but it improved morbidity in patients with chronic HF [10]. In contrast, several observational studies and post hoc analyses of clinical trials have suggested that digoxin may be associated with an increased risk of total and cardiovascular-related death [11–14]. In HF with preserved ejection fraction (HFpEF), the evidence is even more limited and heterogeneous. Recently, chronotropic insufficiency has emerged as a pathophysiological mechanism associated with functional disability and HFpEF progression [15,16]. Along those lines, we hypothesized that, in patients with HFpEF, the prognostic effect of digoxin could be largely dependent on the baseline heart rate. Accordingly, in this study, we aimed to evaluate the association between the use of digoxin after an episode of AHF and the risk of adverse events, relative to heart rate, in patients > 70 years old with HFpEF.

2. Methods

2.1. Study population

Patient data were obtained from the RICA registry, a multicenter, prospective cohort registry of consecutively admitted patients with a diagnosis of AHF. This registry was coordinated by the Heart Failure Working Group of the Spanish Society of Internal Medicine, whose characteristics have been described elsewhere [17].

This study included 1833 patients, older than 70 years, with HF and left ventricular ejection fractions ≥50%, that were treated in 52 centers. HF was diagnosed based on the criteria of the European Society of Cardiology [8]. We retrieved data on demographics, blood pressure, heart rate, body weight and height, ejection fraction, comorbidities, functional status, routine laboratory measurements, and the pharmacological treatment prescribed at discharge. The heart rate was measured at discharge, under resting conditions, in supine decubitus, by performing an electrocardiogram.

2.2. Follow-up and endpoints

The main end-points were all-cause mortality and the composite of mortality and/or HF re-admission. The time to each event was subject to administrative censoring at 1 year. Follow-up consisted of two scheduled visits, one at 3 months and one at 1 year. Ascertainment of endpoints was performed by investigators blinded to both exposures (digoxin treatment and heart rate). The interactions between treatment and heart rate were evaluated for the risk of either outcome in a survival analysis.

2.3. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or the median (interquartile range) per variable distribution. Discrete variables are presented as percentages. Baseline characteristics were compared between treatment groups with either the unpaired *t-test*, or the chi-squared test, as appropriate.

Cox proportional hazard regressions were used to determine the simultaneously-adjusted effects of the digoxin × heart rate interaction on both outcomes. Each model included the following covariates: age (years), gender, Charlson Index, systolic blood pressure (SBP; mmHg), hemoglobin level (Hb; g/dL), the estimated glomerular filtration rate, based on the Modification of Diet in Renal Disease (eGFR-MDRD) formula (ml/min/m^2), use of diuretics, use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), use of spironolactone, and the use of beta-blockers. The linearity assumption (or best functional form) for continuous variables was tested with the multivariable fractional polynomials (FP) method [18]. For mortality and the composite outcome, the FP for heart rate was FP [−2]; other continuous covariates met the linearity assumption. Risk estimates from the Cox models are presented as hazard ratios (HR) with 95% CIs. Because the effect of digoxin varied with heart rate values, HRs were plotted along the continuum of the polynomial-transformed heart rate. Harrell C-statistics was used as the metric for model performance.

We set a two-sided p value of < 0.05 as the threshold for statistical significance. Stata 14.2 (Stata Statistical Software, Release 14 [2015]; StataCorp LP, College Station, TX, USA), was used to perform the main analysis.

3. Results

3.1. Baseline characteristics of the population

The mean age of the cohort was 82.3 ± 5.5 years; 1174 were women (64%), 1629 (88.9%) showed hypertensive etiology and, 1135 (61.9%) had atrial fibrillation. Of the total sample, 401 patients (22%) received digoxin treatment at discharge, and of these, 343 (85.5%) exhibited atrial fibrillation. The median dose of digoxin was 0.20 mg/daily (0.125–0.25) in those receiving digoxin. The mean heart rate upon discharge was 86 ± 22 bpm.

The baseline characteristics of patients treated with or without digoxin are described in Table 1. Briefly, patients treated with digoxin were more often women with atrial fibrillation, better renal function, and a worse functional class. Moreover, they were less likely to have a history of myocardial infarction, dyslipidemia, tobacco use, peripheral artery disease, or a high Charlson Index score of comorbidity. Regarding treatment at discharge, patients treated with digoxin more often received diuretics, ACEI or ARB II, and spironolactone, and less often received beta-blockers (Table 1).

3.2. Clinical endpoints

3.2.1. All-cause death

At the 1-year follow-up, 375 deaths (20.5%) were registered. The rate of all-cause mortality for the entire cohort was 2.61 per 10 person-years. Patients treated with digoxin showed higher rates of death than those treated without digoxin (3.21 vs. 2.44 per 10 person-years, $p = .019$). After comprehensive multivariate adjustments, treatment with digoxin, as the main exposure, remained associated with an increased risk of death (HR = 1.46, 95% CI:1.16–1.85, $p = .001$).

The multivariable analysis also revealed that the effect of digoxin on mortality showed a negative curvilinear relationship with heart rate (interaction p-value = .0073) (Fig. 1a). Indeed, digoxin was independently associated with a higher risk of death among patients with lower heart rates (Fig. 1a). The predicted hazard ratios for specific heart rate ranges are shown in Table 2. For instance, at a heart rate of 50 bpm, patients treated with digoxin showed a 3.38-fold increased risk of death over those treated without digoxin. In contrast, this effect was insignificant at heart rate values of 90–100 bpm. In an analysis stratified by the type of rhythm (atrial fibrillation vs. no atrial fibrillation; Supplementary Table 1), the effect of digoxin remained significant –and heart rate dependent – in patients with atrial fibrillation (Fig. 1b). In patients without atrial fibrillation, despite a similar association between heart rate and risk of death, the effect of digoxin was insignificant (Fig. 1c).

In a sensitivity analysis, evaluating the direction and magnitude of these findings across digoxin doses, we found that the deleterious effect of digoxin at lower heart rates were also found in patients receiving

Table 1
Baseline patient characteristics.

Variable	Total (n = 1833)	Digoxin treatment (n = 401)	No digoxin treatment (n = 1432)	p
Demographic data				
Age, years, mean (SD)	82.27 (5.5)	82.24 (5.3)	82.3 (5.5)	0.90
Sex, woman (%)	1174 (64)	284 (70.8)	890 (62)	0.001
Clinical background				
Hypertension (%)	1629 (88.9)	344 (85.8)	1285 (89.7)	0.03
Diabetes mellitus (%)	930 (51)	209 (52.1)	721 (50.35)	0.53
Ischemic heart disease (%)	305 (16.6)	41 (10.2)	264 (18.4)	< 0.001
Ischemic and hypertensive (%)	283 (15.4)	37 (9.2)	256 (17.2)	< 0.001
Atrial fibrillation (%)	1135 (61.9)	343 (85.5)	792 (55.3)	< 0.001
Dyslipidemia (%)	860 (46.9)	159 (39.6)	701 (49.5)	0.001
COPD (%)	427(23.3)	94 (23.4%)	333 (23.2)	0.94
Cancer (%)	213 (11.6)	39 (9.7)	174 (12.1)	0.18
Peripheral arteriopathy (%)	182 (9.9)	28 (7)	154 (10.75)	0.03
Stroke (%)	276 (15)	67 (16.7)	209 (14.6)	0.29
Smoker (%)	523 (28.3)	98 (24.4)	425 (29.7)	0.04
Charlson index, mean (SD)	3.0 (2.5)	2.6 (2.3)	3.1 (2.5)	< 0.001
Clinical and laboratory				
NYHA class, mean (SD)	2.3 (0.7)	2.4 (0.7)	2.3 (0.7)	< 0.001
Barthel index, mean(SD)	79.96 (22.6)	80 (22.8)	79.9(22.6)	0.94
BMI, kg/m^2, mean (SD)	29.2 (5.5)	29.0 (5.5)	29.3 (5.5)	0.38
SBP, mmHg, mean (SD)	140.7 (26.9)	138.1 (25.9)	141.4 (27.2)	0.03
DBP, mmHg, mean (SD)	74.7 (16.0)	75.8 (16.4)	74.4 (15.9)	0.111
Heart rate, bpm, mean (SD)	85.9 (22.2)	93.5 (25.6)	83.8 (20.6)	< 0.001
Hemoglobin, g/dL, mean (SD)	11.8 (2.0)	11.9 (2.0)	11.8 (2.0)	0.12
eGFR, mL min/1.73 m^2, mean (SD)	56.2 (24.8)	59.8 (22.7)	55.2 (25.3)	< 0.001
Sodium, mEq/L, mean (SD)	138.7 (5.9)	139.0 (4.5)	138.6 (6.2)	0.13
LVEF, mean (SD)	61.9 (8.1)	61.5 (7.7)	62 (8.2)	0,19
Treatment				
Diuretics (%)	1602 (87.4)	378 (94.3)	1224 (85.5)	< 0.001
ACEIs/ARBs (%)	1225 (66.8)	286 (71.3)	939 (65.6)	0.03
Spironolactone (%)	394 (19.9)	97 (24.2)	267 (18.6)	0.01
Beta-blockers (%)	904 (49.3)	156 (38.9)	748 (52.2)	< 0.001
Statins (%)	699 (38.1)	111 (30.2)	578 (40.36)	< 0.001
Anticoagulation (%)	888 (48.4)	296 (73.8)	592 (41.3)	< 0.001
Aspirin (%)	461 (25.1)	60 (15.0)	401 (28)	< 0.001

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NYHA, New York heart association; SBP, systolic blood pressure; SD, standard deviation.

doses below and above the median doses (Supplementary Fig. 1).

3.2.2. *Composite of death and/or re-hospitalization for AHF*

During the 1-year follow-up, 684 (37.3%) composite endpoints were ascertained; thus, the incidence rate for the entire cohort was 5.52 per 10 person-years. The rates of this composite endpoint were higher in those treated with digoxin than in those treated without digoxin (6.72 vs. 5.18 per 10 person-years, p = .003). In the multivariate analysis, digoxin treatment was associated with a higher risk of 1-year death/re-hospitalization (HR = 1.35, 95% CI:1.13–1.61, p = .001).

The multivariable analysis also revealed that the effect of digoxin on the composite endpoint varied in a negative curvilinear relationship with heart rate (interaction p-value = .0303). Treatment with digoxin was deleterious in patients with lower heart rates, but had a neutral effect in patients with higher rates (Fig. 2a). The predicted HRs for specific heart rate ranges are shown in Table 2. In an analysis stratified

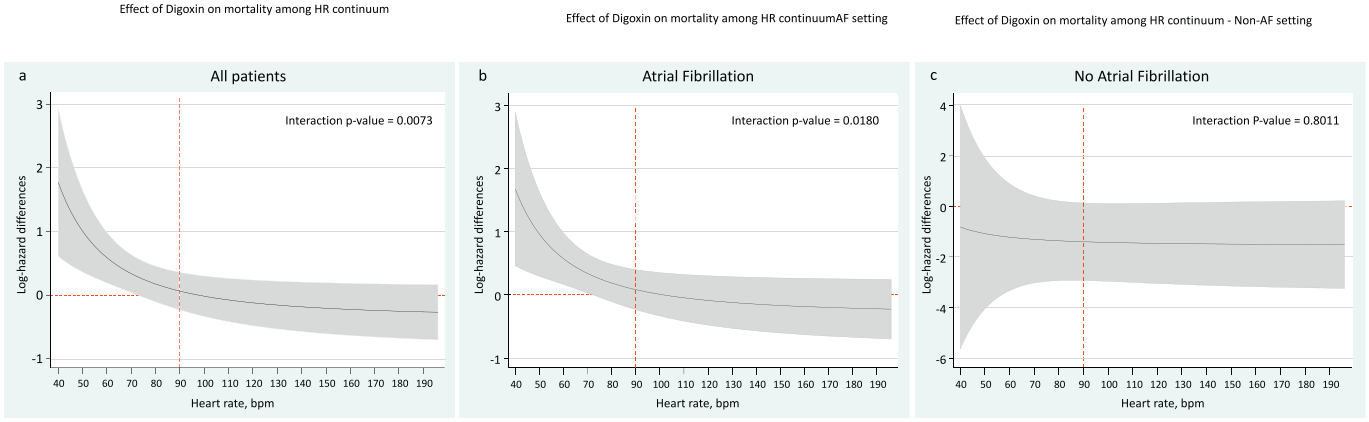

Fig. 1. Digoxin and mortality across heart rate. Curves show the effects of digoxin on mortality across the heart rate continuum in the whole sample (A), in patients with atrial fibrillation (B) and in those without atrial fibrillation (C). Analyses were adjusted for age, gender, Charlson Index, SBP (mmHg), Hb (g/dL), eGFR (ml/min/m2), use of diuretics, use of ACE inhibitors/ARB, use of spironolactone, and use of beta-blockers. Heart rate was modeled with two fractional polynomials: FP [-2]. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; SBP, systolic blood pressure.

Table 2
Hazard ratios of digoxin treatments for specific heart rate ranges (indicated with upper cut-off values).

		All-cause mortality				Composite Endpoint			
Digoxin	Heart rate (bpm)	HR	95% CI		P-value	HR	95% CI		P-value
1 vs. 0	50	3.38	1.66	6.90	0.001	2.40	1.38	4.15	0.002
1 vs. 0	70	1.71	1.31	2.24	0.000	1.51	1.23	1.85	0.000
1 vs. 0	90	1.29	1.00	1.67	0.048	1.24	1.03	1.50	0.022
1 vs. 0	100	1.19	0.89	1.59	0.230	1.18	0.95	1.45	0.127
1 vs. 0	120	1.07	0.76	1.51	0.693	1.09	0.85	1.41	0.481
1 vs. 0	150	0.98	0.66	1.46	0.928	1.03	0.77	1.38	0.835

AF, atrial fibrillation; bpm, beats per minute; CI, confidence interval; HR, hazard ratio.

by atrial fibrillation status (Supplementary Table 2), the effect of digoxin remained significant – and heart rate dependent – in patients with atrial fibrillation (Fig. 2b) but not in those without atrial fibrillation (Fig. 2c). Likewise, the increased risk of the composite endpoint attributable to digoxin at lower heart rates was also found in patients taking doses below and above median (Supplementary Fig. 2).

4. Discussion

To the best of our knowledge, this study was the first to explore the effect of digoxin treatment relative to heart rate in patients with HFpEF that were recently discharged after AHF. We found that digoxin was associated with an increased risk of clinical adverse events in this population, but remarkably, the effect was strongly dependent on heart rate. A neutral effect was found at higher heart rates, and a deleterious effect was observed at lower heart rates.

To date, the indications for the use of digoxin in HF are limited to patients with HFrEF (class of recommendation IIb) [8] and for heart rate control in patients with atrial fibrillation [9]. However, the evidence of its effects in patients with HFpEF remains scarce and heterogeneous. In this regard, the most relevant analysis was a post-hoc subanalysis of the DIG clinical trial [10] in an ambulatory older population with diastolic heart failure and sinus rhythm [2]. In that study, during a median follow-up of 37 months, digoxin had no effect on mortality or on cardiovascular-related or all-cause hospitalizations. Conversely, in the same population, it was observed that the group of patients that received digoxin had a higher risk of re-hospitalization at 30 days [19]. However, no solid data are available from studies that evaluated the prognostic effects of digoxin in an unselected, real-life cohort of older patients with HFpEF, most with atrial fibrillation [20].

The optimal heart rate range in patients with HFpEF remains uncertain. Bertomeu-González et al. [21] studied a cohort of 1111 patients with AHF that exhibited HFpEF or HFrEF. They found a differential effect of heart rate on mortality, according to the presence of sinus rhythm or atrial fibrillation. Those authors found a positive linear effect of heart rate on mortality among patients with sinus rhythm, but a negative linear association among patients with atrial fibrillation (52.4% with HFpEF). A recent meta-analysis [22] studied patients with HFpEF and HFrEF, both in sinus rhythm and with atrial fibrillation. They found that higher heart rates were associated with a worse prognosis among patients with HFpEF and sinus rhythm. In contrast, among patients with atrial fibrillation, a higher heart rate did not confer a worse prognosis. Along the same lines, in a subgroup analysis of the I-PRESERVE study, higher heart rates were associated with a higher risk of death and re-admission among patients in sinus rhythm, but not among those with atrial fibrillation [23].

The present analysis was performed with a very old cohort, and most patients had atrial fibrillation. We provided robust evidence that the prognostic effect of digoxin depended on the baseline heart rate. We observed a negative prognostic impact at lower heart rates and a neutral effect at high rates. This differential effect was particularly notable in patients with atrial fibrillation; digoxin had a neutral effect in patients in sinus rhythm. Currently, little evidence is available to support this association. However, there are a number of mechanisms that may, at least in part, explain our findings. We speculate that, in a non-negligible subgroup of patients with HFpEF, digoxin may exacerbate chronotropic incompetence and increase central systolic pressure. This mechanism has been increasingly recognized and has gained attention in recent years.

In patients with AHF, tachycardia is a physiological, beneficial compensatory response, which contributes to an increase in cardiac output. Chronotropic incompetence is the inability of the heart to increase heart rate adequately. In patients with HFpEF and atrial fibrillation, the lack of this compensatory mechanism might result from a dysfunctional conduction system and/or adrenergic denervation. Indeed, the pathophysiology of an altered heart rate response is complex. It has been associated with a reduction in β receptor density [24] and with β receptor desensitization, despite the presence of increased levels of circulating amines [25] and sinus node remodeling [26]. We postulate that chronotropic insufficiency in patients with HFpEF and atrial fibrillation may be more prevalent than anticipated. In this scenario, a positive inotropic and negative chronotropic drug, such as digoxin, could exacerbate this disorder. Furthermore, when patients with HFpEF are in situations of intense diastolic compromise, cardiac output

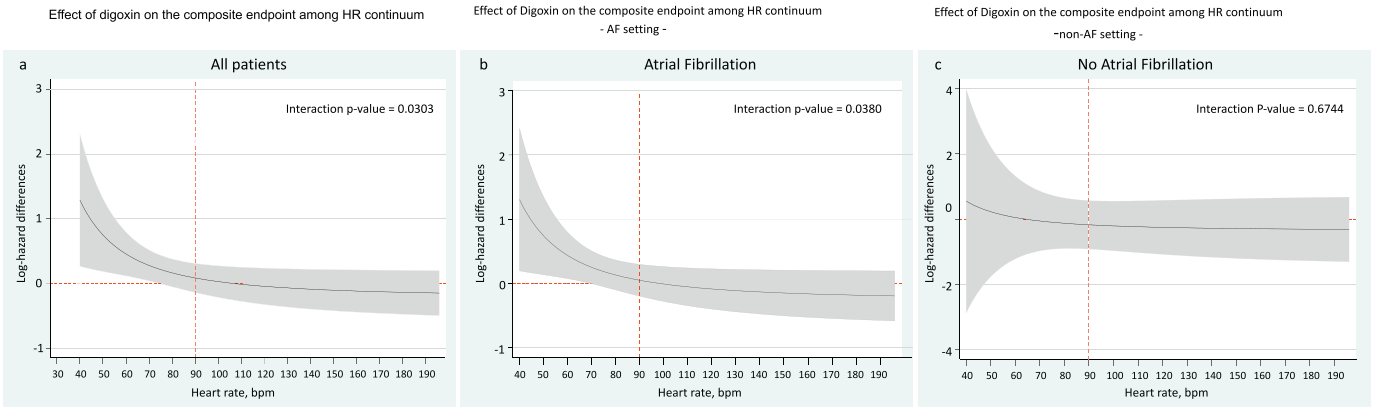

Fig. 2. Digoxin and the composite of death/HF-readmission across heart rate. Curves show the effects of digoxin on mortality across the heart rate continuum in the whole sample, (A), with atrial fibrillation and (B) without atrial fibrillation (C). Analyses were adjusted for age, gender, Charlson Index, SBP (mmHg), Hb (g/dL), eGFR (ml/min/m2), use of diuretics, use of ACE inhibitors/ARB, use of spironolactone, and use of beta-blockers. Heart rate was modeled with two fractional polynomials: FP [-2]. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; SBP, systolic blood pressure.

is strongly dependent on heart rate. Thus, in these situations, progressive bradycardia will lead to a reduction in cardiac output [27,28]. In addition, when a negative chronotropic drug decreases heart rate, the reflected pulse wave may return during ventricular systole. The resultant ventricular-vascular maladjustment increases the central systolic pressure by increasing the ventricular filling pressures. This effect has been observed in several studies on hypertensive populations, where a central pressure elevation associated with beta-blockers translated into an increased risk of cardiovascular events, such as myocardial infarction, stroke, and HF [29]. A similar, or even greater deleterious effect of increasing the central systolic blood pressure may occur with the use of a heart rate-lowering inotropic agent, such as digoxin, in patients with HFpEF.

Finally, our cohort comprised a very old population with HF. Previous reports, mainly in patients with HFrEF, have pointed out a U-shaped curve along the heart rate continuum, with a nadir at 67 beats/min and increased risk at both ends [30]. Thus, it is advisable that, in older patients with HF, regardless of whether the EF is preserved, low heart rates should not be a goal, and a more lenient approach should be considered.

4.1. Study limitations

First, it should be noted that, because this study was observational, it had limitations inherent to the study design. Importantly, with this type of design we cannot infer causality. Second, we used heart rate and other covariates measured at baseline and they were not longitudinally assessed throughout the study. Third, despite thorough adjustments of our multivariable analyses, we could not rule out residual confounding and the influence of unmeasured confounders. For instance, the lack of routine assessment of diastolic parameters and natriuretic peptides precluded to evaluate the influence of them on digoxin-prognostic effect. Fourth, our findings are not generalizable to the whole spectrum of patients with HFpEF. Fifth, we did not measure the treatment compliance during follow-up. Finally, based on our present data, we could not unravel the pathophysiological mechanism underlying the observed association.

5. Conclusions

This study demonstrated that, following an AHF hospitalization, digoxin prescription for older patients with HFpEF, and mostly with atrial fibrillation, was associated with a higher risk of adverse events. This effect was strongly dependent on the baseline heart rate, raising questions about the value of digoxin in this challenging clinical scenario. Further studies are needed to confirm our present findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.10.010.

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Conflict of interest statement

There is no conflict of interests.

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Appendix A. Appendix

RICA Registry members

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