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ORIGINAL ARTICLE

Impact of digoxin on risk of death in heart failure patients treated with β-blockers. Results from Polish part of ESC Heart Failure Long-Term Registry

Jacek Migaj[1], Marta Kałużna-Oleksy[1], Jadwiga Nessler[2], Grzegorz Opolski[3], Marisa G. Crespo-Leiro[4], Aldo P. Maggioni[5], Stefan Grajek[1], Piotr Ponikowski[6], Jarosław Drożdż[7], Ewa Straburzyńska-Migaj[1]

[1]1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

[2]Clinical Department of Coronary Disease and Heart Failure, Jagiellonian University Medical College, Krakow, Poland

[3]1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

[4]Unidad Insuficiencia Cardiaca Avanzada y Trasplante Cardiaco Servicio de Cardiologia, Instituto Universitario de Ciencias de la Salud, A Coruna, Spain

[5]ANMCO Foundation for Your Heart, Florence, Italy

[6]Department of Cardiology, Wroclaw Medical University, 4th Military Hospital, Wroclaw, Poland

[7]Department of Cardiology, Medical University of Lodz, Lodz, Poland

Abstract

Background: Digoxin is used in the treatment of atrial fibrillation (AF) and heart failure (HF). It was reported to increase the risk of death in HF. Studies on digoxin are based mainly on patients treated some years ago, before the era of common β-blocker use.

Aim: This study aims to show the influence of digoxin in a modern cohort of HF patients on top of the contemporary guideline-directed treatment.

Methods: This study retrospectively analyses the Polish part of the European Society of Cardiology Heart Failure Long-Term Registry. It includes 912 patients treated for HF between February 2012 and January 2013, and followed until May 2014. At baseline, 19.1% took digoxin, 89.6% angiotensin convertase enzyme inhibitors or angiotensin receptor blockers, 91.9% β-blockers, and 69.4% mineralocorticoid receptor antagonists.

Results: Digoxin is associated with increased risk of death after adjustment for significant covariates in patients who have HF with reduced ejection fraction (HFrEF) but no AF history (hazard ratio [HR] 2.52, 95% confidence interval [CI] 1.23–5.19; p = 0.011), and it does not influence significantly the risk of hospitalisation (adjusted HR 1.46, 95% CI 1.05–1.72; p = 0.11). Digoxin use shows no significant association with the risk of death or hospitalisation in patients with AF and HFrEF or HF with preserved ejection fraction (HFpEF). Patients on digoxin present a significantly worse clinical status with lower left ventricular ejection fraction and higher New York Heart Association class, and fewer of them received the guideline-directed treatment.

Conclusions: Digoxin is associated with increased risk of death in HFrEF patients without AF history receiving the guideline-directed treatment. Digoxin seems to be employed in patients with worse clinical status, which may at least partially explain its association with increased risk of death.

Key words: β-blockers, digoxin, heart failure, hospitalisations, mortality

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INTRODUCTION

Digoxin is an old drug used in the treatment of atrial fibrillation (AF) and heart failure (HF) to slow down heart rate and improve symptoms in HF. According to the current European Society of Cardiology (ESC) guidelines "it may be considered in patients in sinus rhythm with symptomatic HF with reduced ejection fraction (HFrEF) to reduce the risk of hospitalisation (both all-cause and HF hospitalisations)" [1], which is based on

Address for correspondence:
Jacek Migaj, MD, 1st Department of Cardiology, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, tel: +48 602 448 377, e-mail: jmigaj@ump.edu.pl

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the Digitalis Investigation Group (DIG) study [2]. Moreover, "in patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued" [1].

The DIG study, the only randomised controlled trial of digoxin, was published in 1997, and the ESC guidelines on treatment of acute and chronic HF have changed significantly since then. We have witnessed growing numbers of patients treated with β-blockers, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and implantable cardioverter-defibrillators (ICDs) or cardiac resynchronisation therapy (CRT). During these 20 years, several researchers published data that provoked discussion about the safety of treatment with digoxin. The most recent studies questioning the safety of treatment are those by Vamos et al. [3], Madelaire et al. [4], Qureshi et al. [5], Al-Khateeb et al. [6], and Katz et al. [7]. Other authors showed no influence of digoxin on outcomes of HF patients (e.g. Chamaria et al. [8] and Ziff et al. [9]) or confirmed the initial discovery that digoxin decreased the risk of hospitalisation in HF patients (e.g. Andrey et al. [10], Ahmed et al. [11], and Ziff et al. [9]); some even showed improved outcomes of patients on digoxin [11].

Although these findings provoked a vivid discussion, the patients investigated by the abovementioned researchers participated in studies conducted several years ago, and therefore included relatively low percentages of patients on β-blockers (26%–64%), ACEI or ARB (49%–93%), and MRA (10%–29%), with the exceptions of the studies by Al-Khateeb et al. [6] and Erath et al. [12]. As stated in the ESC guidelines on treatment of acute and chronic HF, "digoxin's effect on top of β-blockers has never been tested" [1].

The aim of the study presented herein was to show the effect of treatment with digoxin on the risk of mortality and hospitalisations in a modern cohort of patients with HF, chosen to reflect the current ESC guidelines on usage of digoxin, on top of contemporary guideline-directed treatment.

METHODS

ESC Heart Failure Long-Term Registry

The ESC Heart Failure Long-Term Registry was a large prospective study of HF patients. The Polish part of the registry included 1126 patients (765 inpatients and 361 outpatients) treated for chronic or acute HF between February 2012 and March 2013, and followed until May 2014. The mean follow-up was 332 days (range 14– 817 days). Evaluation of these patients was based on medical history, physical examination, and laboratory tests taken at baseline visit and after 12 months. The inpatients were evaluated both on admission to hospital and on discharge. The primary endpoint was death, and the secondary endpoint was HF hospitalisation. The registry was approved by the appropriate ethics review board at every site that included patients into this registry.

Analysis of digoxin use

This was a retrospective analysis of the Polish part of the ESC Heart Failure Long-Term Registry. We included both outpatients and inpatients (of the latter only the data from discharge status were taken into account) in our analysis. Complete data on survival and rehospitalisations were available for 1030 patients of the registry; among them, 174 received digoxin at baseline and took it throughout the follow-up, and 738 did not take digoxin at all; these two groups were included in further analyses (912 patients in total). The rest of the patients ($n = 118$) had digoxin employed or discontinued during the follow-up, and they were excluded from further analyses to rule out the bias from unknown duration of treatment. The patients were considered to have HFrEF when the ejection fraction was $\leq 45\%$, and HF with preserved ejection fraction (HFpEF) when the ejection fraction was $> 45\%$.

Statistical analysis

Statistical analysis was performed using STATISTICA 12 (Tibco Software Inc., Palo Alto, CA, USA). Probability distribution of continuous variables was tested with Lillefors and Shapiro-Wilk tests. The distribution of all the investigated variables was found non-normal; hence, the Mann-Whitney U test was used. The χ^2 test was used for categorical variables, with Yates's correction where applicable. Univariate regression models, log rank tests, and Kaplan-Maier plots were used to assess unadjusted survival. Multivariate analysis of survival was performed using Cox proportional hazard regression models with adjustment for the parameters that significantly differed between the survivors and non-survivors (age, New York Heart Association [NYHA] class, AF history, chronic kidney disease [CKD], left ventricular ejection fraction [LVEF], B-type natriuretic peptide [BNP], blood haemoglobin concentration at presentation, ICD/CRT-D therapy, and ACEI/ARB > 50% of optimal dose). The data are expressed as mean values with standard deviation for continuous variables, and percentages for categorical variables. A p value of < 0.05 was considered statistically significant for all the tests.

RESULTS

General characteristics

Overall, 19.1% of patients were treated with digoxin. It is worth noting that nearly all the patients took ACEI or ARB (91.5% HFrEF and 84.5% HFpEF), β-blockers (95.4% HFrEF and 82.8% HFpEF), and MRA (76.0% HFrEF and 52.4% HFpEF). There were also 18 patients on ivabradine (2%). Baseline statistics are shown in Table 1.

The percentage of patients receiving digoxin increased with NYHA class from I to IV (4.6%, 15.1%, 30.5%, and 35.7%, respectively; $p < 0.001$). Patients with HFrEF were more likely

Table 1. Baseline characteristics

General	HFrEF (n = 653)			HFpEF (n = 233)			Total (n = 912)		
	On digoxin (n = 138)	No digoxin (n = 515)	p	On digoxin (n = 31)	No digoxin (n = 202)	p	On digoxin (n = 174)	No digoxin (n = 738)	p
Age [years]	**61 (14)**	**64 (13)**	**0.043**	**77 (10)**	**72 (12)**	**0.018**	**64 (15)**	**66 (13)**	**0.047**
NYHA class	**2.5 (0.6)**	**2.2 (0.6)**	**< 0.001**	**2.5 (0.5)**	**2.1 (0.6)**	**0.002**	**2.5 (0.6)**	**2.2 (0.6)**	**< 0.001**
Non-survivors	**33 (24%)**	**60 (12%)**	**< 0.001**	7 (23%)	25 (12%)	0.12	**40 (23%)**	**88 (12%)**	**< 0.001**
Hospitalised	**72 (52%)**	**193 (38%)**	**0.002**	**7 (23%)**	**86 (43%)**	**0.034**	82 (47%)	288 (39%)	0.05
Test results									
Haemoglobin [mmol/L]	8.4 (1.3)	8.4 (1.2)	0.95	7.9 (1.1)	8.2 (1.2)	0.22	8.3 (1.3)	8.3 (1.2)	0.72
Serum creatinine [μmol/L]	92 (37)	95 (50)	0.94	83 (28)	88 (44)	0.73	90 (35)	93 (49)	0.72
eGFR [mL/min/1.73 m^2]	86 (33)	84 (31)	0.70	79 (28)	82 (30)	0.51	85 (32)	84 (32)	0.89
BNP [pg/mL]	1570 (2204)	955 (1166)	0.14	491 (452)	355 (409)	0.09	1276 (1944)	783 (1038)	0.06
NT-proBNP [pg/mL]	5632 (7654)	5248 (6810)	0.94	4001 (3585)	2664 (3482)	0.08	5156 (6986)	4584 (6211)	0.62
LVEF [%]	**26 (9)**	**31 (9)**	**< 0.001**	54 (4)	56 (7)	0.08	**31 (14)**	**38 (14)**	**< 0.001**
Comorbidities									
CKD	27 (20%)	126 (25%)	0.23	7 (23%)	42 (21%)	0.82	34 (20%)	173 (23%)	0.27
AF history	**89 (65%)**	**161 (31%)**	**< 0.001**	**28 (90%)**	**89 (44%)**	**< 0.001**	**119 (68%)**	**259 (35%)**	**< 0.001**
Diabetes mellitus	43 (31%)	165 (32%)	0.86	10 (32%)	61 (30%)	0.82	55 (32%)	233 (32%)	0.89
History of malignancy	7 (5%)	14 (3%)	0.16	1 (0.5%)	10 (5%)	0.97	8 (5%)	24 (3%)	0.39
Device therapy									
ICD	**44 (31%)**	**111 (22%)**		0	6 (3%)		**44 (25%)**	**120 (16%)**	**< 0.001**
PM	**5 (4%)**	**25 (5%)**	**< 0.001**	4 (13%)	14 (7%)	0.75	**9 (5%)**	**40 (5%)**	
CRT-P/CRT-D	**26 (19%)**	**40 (8%)**		0	3 (1.5%)		**27 (16%)**	**43 (6%)**	
Medication									
ACEI/ARB	**117 (85%)**	**476 (92%)**	**0.006**	23 (65%)	173 (86%)	0.10	**144 (83%)**	**667 (90%)**	**0.004**
ACEI/ARB > 50% of optimal dose	**64 (55%)**	**327 (69%)**	**0.005**	15 (65%)	130 (75%)	0.30	**82 (57%)**	**468 (70%)**	**0.002**
β-blockers	130 (94%)	493 (96%)	0.45	22 (71%)	171 (85%)	0.06	157 (90%)	682 (92%)	0.34
MRA	**117 (85%)**	**379 (74%)**	**0.006**	**23 (74%)**	**99 (49%)**	**0.009**	**145 (83%)**	**488 (66%)**	**< 0.001**
Amiodarone	17 (12%)	76 (15%)	0.46	1 (3%)	11 (5%)	0.93	18 (10%)	87 (12%)	0.68

Data are shown as mean (standard deviation) or number (percentage). ACEI — angiotensin converting enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin receptor blocker; BNP — B-type natriuretic peptide; CKD — chronic kidney disease; CRT-D — cardiac resynchronisation therapy with ICD function; CRT-P — cardiac resynchronisation therapy; eGFR — estimated glomerular filtration rate; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction; MRA — mineralocorticoid receptor antagonist; NT-proBNP — N-terminal pro–B-type natriuretic peptide; NYHA — New York Heart Association; PM — pacemaker

to receive digoxin than those with HFpEF (21.1% vs. 13.3%; p = 0.009), and they had a significantly worse clinical status with a larger group of patients with NYHA class III/IV compared to HFpEF (32.6% vs. 22.8%; p = 0.005). Prevalence of AF in HFpEF patients was higher than in the HFrEF group (50.2% vs. 38.3%; p = 0.002), and HFrEF patients with AF were more likely to receive digoxin than those with HFpEF and AF (35.6% vs. 23.9%; p < 0.001). The non-survivors used digoxin more often, were older, had a worse clinical status with higher mean NYHA class, more frequent AF history and worse kidney function, and less often received the guideline-directed treatment compared to the survivors (Table 2). There was no difference between the percentages of patients on digoxin who died due to cardiac or non-cardiac causes (31.5% vs. 33%; p = 0.76). The causes of death are shown in Figure 1.

Comparison of patients receiving and not receiving digoxin

The patients on digoxin were younger but they presented a significantly worse clinical status than those who did not receive the drug, they had a lower mean LVEF, a higher death rate, and fewer of them received the guideline-directed treatment (Table 1). To minimise prescription bias, severe HF patients were analysed separately (NYHA III/IV, and HF with LVEF < 25%). Those on digoxin were younger, had a higher

Table 2. Comparison of survivors and non-survivors (all patients)

General	Survivors (n = 784)	Non-survivors (n = 128)	p
Age [years]	65 (14)	72 (11)	< 0.001
NYHA class	2.2 (0.6)	2.5 (0.6)	< 0.001
Aetiology			0.052
Ischaemic	408 (52%)	74 (58%)	
DCM	265 (34%)	30 (23%)	
Other	111 (14%)	24 (19%)	
Test results			
Haemoglobin [mmol/L]	8.4 (1.2)	7.9 (1.2)	< 0.001
Serum creatinine [μmol/L]	90 (45)	109 (54)	< 0.001
eGFR [mL/min/1.73 m^2]	86 (32)	72 (32)	< 0.001
BNP [pg/mL]	682 (740)	1860 (2470)	< 0.001
NT-proBNP [pg/mL]	4040 (5617)	8780 (8870)	< 0.001
LVEF [%]	37 (14)	34 (16)	0.009
Comorbidities			
CKD	148 (18.9%)	59 (46.1%)	< 0.001
AF history	311 (39.7%)	67 (52.3%)	0.009
Diabetes mellitus	238 (30.4%)	51 (39.8%)	0.09
History of malignancy	25 (3.2%)	7 (5.5%)	0.19
Device therapy			
ICD	140 (17.9%)	24 (18.7%)	
PM	37 (4.7%)	12 (9.4%)	0.048
CRT-P/CRT-D	54 (6.9%)	16 (10.9%)	
Medication			
Digoxin	134 (17%)	40 (23%)	< 0.001
ACEI/ARB	707 (90%)	104 (81%)	0.003
ACEI/ARB > 50% of optimal dose	494 (70%)	56 (54%)	0.001
β-blockers	730 (93%)	109 (85%)	0.002
MRA	541 (69%)	92 (72%)	0.51
Amiodarone	85 (11%)	20 (16%)	0.12

Data are shown as mean (standard deviation) or number (percentage). DCM — dilated cardiomyopathy; other abbreviations — see Table 1

death rate, lower LVEF, higher incidence of AF, more ICDs and CRTs, and were more likely to be treated with MRA (Table 3).

The effect of digoxin on hospitalisations and mortality

Treatment with digoxin was associated with increased risk of death (Fig. 2) and hospitalisation in univariate analysis (hazard ratio [HR] 1.35; p = 0.017), but the latter disappeared after adjustment. HFrEF patients without AF presented the highest hazard ratio (Table 4); however, digoxin had no significant influence on the risk of death in HFrEF patients when patients with mild and severe HF (NYHA III/IV, and NYHA I/II, and HF with LVEF < 25%; Table 4) were analysed separately.

The HFrEF patients with AF history showed no significant influence of digoxin on the risk of death or hospitalisation; the same was true for the HFpEF patients with or without AF history.

DISCUSSION

Key findings

Our study shows new evidence that digoxin is independently associated with a higher risk of death in HF patients who receive the contemporary guideline-directed treatment, and that HFrEF patients without AF history demonstrate the highest risk. Furthermore, contrary to other authors, we showed that digoxin has no influence on the risk of mortality and hospitalisations in HF patients with AF history, regardless

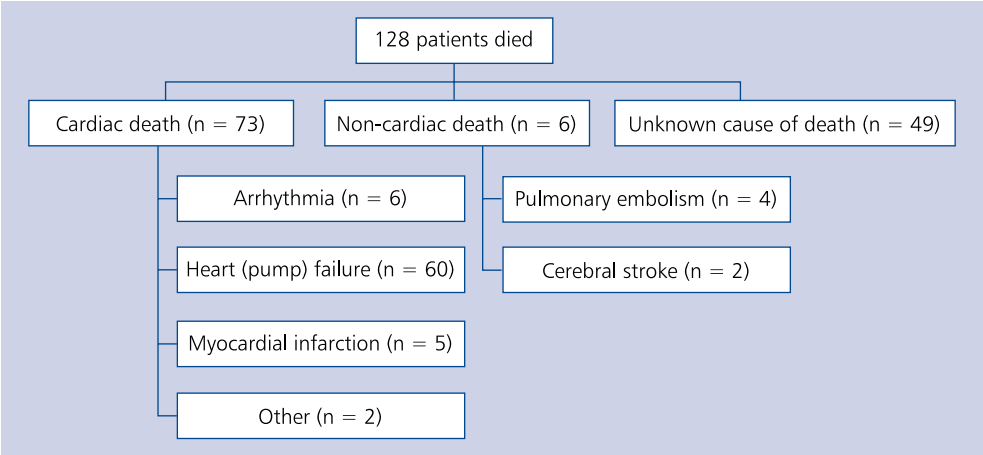

Figure 1. Causes of death (all patients)

Table 3. Comparison of severe heart failure patients receiving and not receiving digoxin

General	NYHA III and IV (n = 273)			LVEF < 25% (n = 253)		
	On digoxin (n = 84)	No digoxin (n = 189)	p	On digoxin (n = 81)	No digoxin (n = 172)	p
Age [years]	**65 (14)**	**68 (12)**	**0.037**	60 (12)	63 (14)	0.08
NYHA class	3.1 (0.2)	3.1 (0.2)	0.68	**2.6 (0.6)**	**2.4 (0.6)**	**0.024**
Non-survivors	**25 (30%)**	**34 (18%)**	**0.029**	**24 (30%)**	**29 (17%)**	**0.019**
Hospitalised	40 (48%)	77 (41%)	0.29	**49 (60%)**	**77 (45%)**	**0.019**
Test results						
Haemoglobin [mmol/L]	8.15 (1.4)	8.05 (1.3)	0.64	8.49 (1.1)	8.40 (1.2)	0.75
Serum creatinine [μmol/L]	95 (42)	107 (75)	0.27	97 (43)	105 (67)	0.24
eGFR [mL/min/1.73 m^2]	83 (34)	76 (32)	0.20	85 (36)	78 (30)	0.32
BNP [pg/mL]	1410 (2253)	996 (1349)	0.38	1826 (2477)	1398 (1146)	0.94
NT-proBNP [pg/mL]	5789 (5461)	7623 (8433)	0.49	5761 (7576)	6599 (6579)	0.15
LVEF [%]	**29 (14)**	**34 (15)**	**0.004**	19 (4)	21 (4)	0.07
Comorbidities						
CKD	22 (26%)	67 (36%)	0.13	19 (23%)	54 (31%)	0.19
AF history	**52 (62%)**	**67 (36%)**	**< 0.001**	**44 (54%)**	**56 (32%)**	**< 0.001**
Diabetes mellitus	29 (35%)	71 (38%)	0.73	27 (33%)	59 (34%)	0.77
History of malignancy	4 (5%)	7 (4%)	0.68	3 (4%)	5 (3%)	0.73
Device therapy						
ICD	**25 (30%)**	**35 (18%)**		33 (41%)	60 (35%)	
PM	**3 (4%)**	**11 (6%)**	**0.002**	**1 (1%)**	**9 (5%)**	**0.033**
CRT-P/CRT-D	**15 (18%)**	**19 (10%)**		18 (22%)	22 (14%)	
Medication						
ACEI/ARB	70 (83%)	152 (80%)	0.57	67 (83%)	156 (91%)	0.07
ACEI/ARB > 50% of optimal dose	35 (50%)	92 (61%)	0.14	34 (51%)	93 (60%)	0.22
β-blockers	75 (89%)	173 (92%)	0.55	78 (96%)	166 (97%)	0.93
MRA	**67 (80%)**	**124 (66%)**	**0.019**	70 (86%)	141 (82%)	0.37
Amiodarone	11 (13%)	26 (14%)	0.88	**10 (12%)**	**44 (26%)**	**0.016**

Data are shown as mean (standard deviation) or number (percentage). Abbreviations — see Table 1

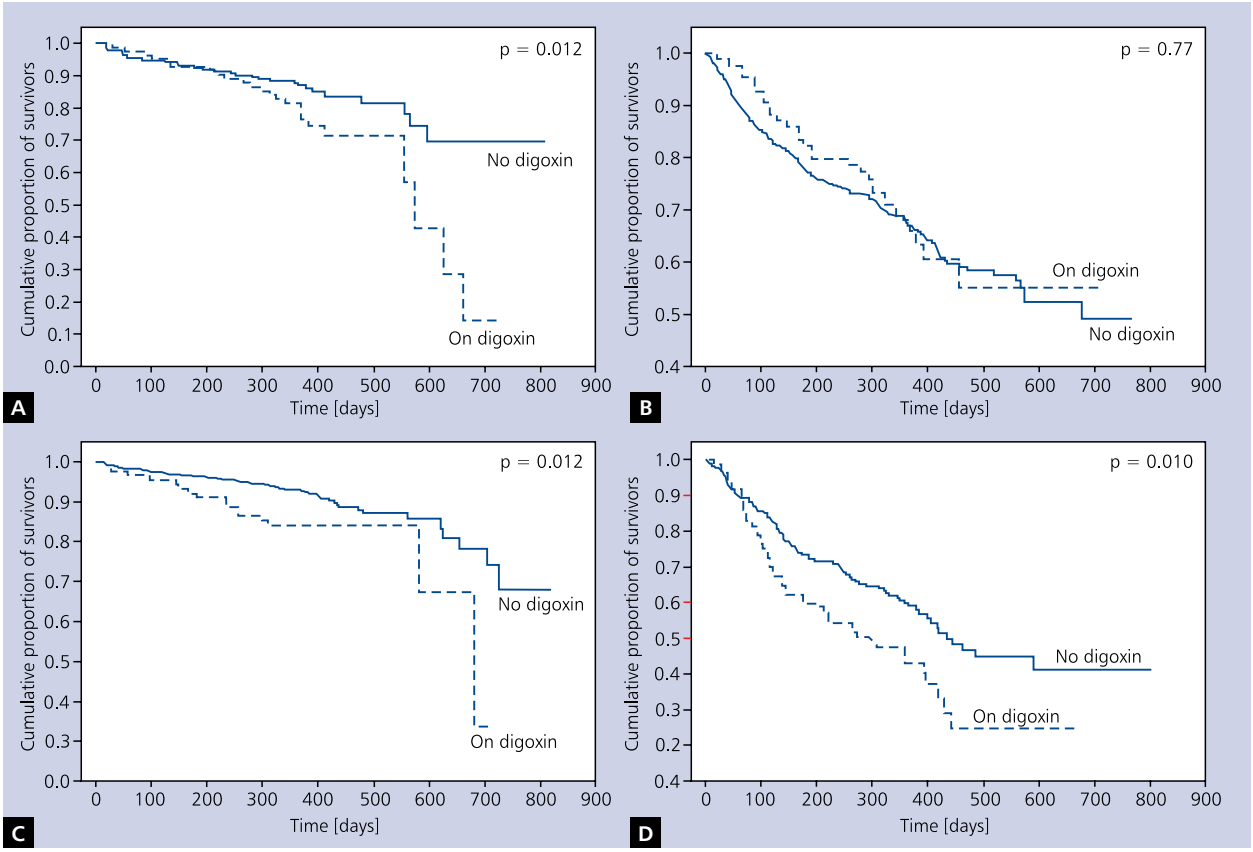

Figure 2. Survival probability and hospitalisation-free survival probability in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) (Kaplan-Meier plot; log-rank p); **A.** Survival probability in HFrEF; **B.** Hospitalisation-free survival probability in HFpEF; **C.** Survival probability in HFpEF; **D.** Hospitalisation-free survival probability in HFrEF

of the type of HF (HFrEF vs. HFpEF) [5, 13–16]. Our study confirms the findings of several authors [3–7, 12, 17, 18] who showed a negative influence of digoxin on the outcomes of HF patients, and contradicts others who showed a neutral [9, 19] or a positive effect of digoxin [2, 10, 20–23]. Our analysis suggests that worse clinical state of patients treated with digoxin might be at least partially responsible for the observed association with increased risk of death, which was mentioned earlier by only a few authors [24, 25].

To our knowledge, this is the first study including patients who received the guideline-directed treatment (β-blockers 91.9%, ACEI or ARB 89.6%, and MRA 69.4%) and who were treated with digoxin throughout the follow-up period. This is contrary to numerous other studies on digoxin, which analysed patients treated with digoxin throughout the follow-up but without the other modern guideline-directed treatment [18, 26], or which included patients treated according to the modern ESC guidelines but receiving digoxin only "at some point of the follow-up/at baseline" [6, 12], or which did not include patients with guideline-directed treatment nor analysed the length of treatment with digoxin [13–16]. Our study also seems to analyse the most up-to-date cohort of patients, followed between 2012 and 2014.

Digoxin in heart failure

Our study has shown that digoxin is independently associated with a higher risk of all-cause mortality with adjusted HR 1.87 in a group of 912 HF patients. Two other recent studies (both published in 2016) included patients with modern treatment, similarly to our study (very high percentages of β-blocker-, ACEI/ARB-, and MRA-users). The retrospective analysis by Erath et al. [12] of a group of 1020 patients with ICD implanted as primary or secondary prevention and with or without AF, followed for 10 years, showed adjusted HR of 1.65; similarly, Al-Khateeb et al. [6] analysed 1075 chronic HF patients with or without AF, with LVEF < 45%, chosen using propensity score matching, and showed adjusted HR of 1.74. These two studies showed a harmful effect of treatment with digoxin in heterogeneous groups of patients. To rule out such a bias in our investigation, we analysed a subgroup of patients treated with digoxin according to the current ESC guidelines, i.e. with HFrEF and without AF, and we showed

Table 4. Adjusted hazard ratios (death risk)

	HFrEF (n = 653)		HFpEF (n = 233)		HFrEF without AF (n = 403)		LVEF < 25% (n = 253)		HFrEF with NYHA III or IV (n = 213)		HFrEF with NYHA I and II (n = 440)	
	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
Digoxin	**0.013**	**1.88 (1.14–3.08)**	0.96	1.02 (0.38–2.76)	**0.011**	**2.52 (1.23–5.19)**	**0.017**	**2.12 (1.14–3.95)**	0.09	1.76 (0.89–3.46)	0.12	1.76 (0.85–3.62)
ACEI/ARB > 50% of optimal dose	**0.007**	**0.54 (0.35–0.85)**	0.38	1.54 (0.58–4.08)	0.06	0.56 (0.31–1.01)	**0.010**	**0.44 (0.24–0.82)**	0.23	0.66 (0.34–1.28)	**0.043**	**0.52 (0.28–0.98)**
Age	**< 0.001**	**1.04 (1.01–1.06)**	**0.002**	**1.07 (1.03–1.12)**	**< 0.001**	**1.05 (1.02–1.09)**	**0.009**	**1.04 (1.00–1.07)**	0.31	1.01 (0.99–1.04)	**0.001**	**1.05 (1.02–1.09)**
AF history	0.44	1.19 (0.76–1.87)	0.14	1.91 (0.82–4.51)			0.55	1.19 (1.16–3.94)	0.63	1.16 (0.62–2.17)	0.57	1.09 (0.58–2.09)
CKD	**0.008**	**1.84 (1.17–2.90)**	**< 0.001**	**3.79 (1.71–8.37)**	0.30	1.39 (0.74–2.65)	**0.015**	**2.14 (0.57–1.62)**	**0.033**	**1.92 (1.03–3.61)**	0.19	1.58 (0.79–3.15)
NYHA class	0.08	1.40 (0.97–2.03)	0.15	1.59 (0.85–2.99)	0.20	1.40 (0.84–2.35)	0.89	0.97 (0.57–1.62)	0.08	2.61 (0.89–7.67)	0.89	0.92 (0.27–3.10)
Haemoglobin	0.42	0.93 (0.78–1.11)	0.20	0.81 (0.59–1.11)	0.26	0.86 (0.67–1.11)	0.53	0.93 (0.73–1.17)	0.89	1.02 (0.82–1.26)	0.24	0.82 (0.59–1.14)
LVEF	**0.006**	**0.97 (0.94–0.99)**	**0.032**	**0.94 (0.89–0.99)**	**0.033**	**0.96 (0.93–0.99)**	0.21	0.96 (0.89–1.02)	0.22	0.98 (0.94–1.01)	**0.010**	**0.95 (0.92–0.99)**
BNP	**0.011**	**1.00 (1.00–1.00)**	**0.017**	**1.00 (1.00–1.00)**	0.15	1.00 (0.99–1.00)	0.07	1.00 (0.99–1.00)	**0.008**	**1.00 (1.00–1.00)**	0.95	1.00 (0.99–1.00)
ICD/CRT-D	0.61	0.88 (0.56–1.41)			0.79	0.92 (0.49–1.72)	0.68	1.13 (0.62–2.06)	0.48	0.79 (0.41–1.52)	0.39	1.24 (0.63–2.46)

CI — confidence interval; HR — hazard ratio; other abbreviations — see Table 1

that such patients are especially at risk of death when using digoxin (adjusted HR 2.52).

Contrary to our findings, many authors demonstrated a positive impact of digoxin on the risk of mortality and hospitalisation. They showed that low serum concentrations of digoxin were associated with improved outcomes (0.5–0.7 ng/mL, HR 0.77 [27] or 0.5–0.9 ng/mL, HR 0.77 [20]), and that digoxin reduced one-year mortality (HR 0.89) and hospitalisation risk (HR 0.82) in HF patients treated with ACEI [11]. These authors attributed the increased mortality of patients on digoxin to its toxicity, i.e. high doses and high serum concentrations. Unfortunately, digoxin serum concentrations and the exact doses were not available to our analysis. There were no differences in the incidence of CKD between the patients receiving or not receiving digoxin, but the non-survivors presented CKD significantly more often. Thus, we cannot rule out the influence of overly high digoxin concentrations on the outcomes of our patients.

Some authors looked for specific populations benefiting from digoxin use, e.g. HF patients with NYHA class III/IV and LVEF < 25% [28], while others looked for patients who were especially at risk when treated with digoxin, e.g. women with hypertension [29]. Digoxin was reported to decrease the risk of readmission to hospital [30] and even to improve kidney function [21]. However, all this evidence bases mainly on the DIG trial and its post hoc analyses. We found only one study showing a positive influence of digoxin on mortality and morbidity, which was not based on the DIG data [10]. All the abovementioned studies were conducted some years ago, which makes their conclusions questionable in the era of wide use of β-blockers.

Several meta-analyses of the available data were conducted and gave various results. Chamaria et al. [8] showed that digoxin is not associated with increased mortality when used for rate control in AF and HF patients. Ziff et al. [9] showed a neutral effect of digoxin on mortality and a positive effect on hospital readmissions. Two other authors showed an increased mortality risk in HF patients (HR 1.14 [3] and HR 1.21 [5]). However, these meta-analyses have the same disadvantages as the studies they include, i.e. lack of contemporary medication and heterogeneous groups of patients (combined HFrEF and HFpEF, and both with and without AF).

Our aim was to investigate the use of digoxin in HF patients receiving an up-to-date guideline-recommended treatment, especially β-blockers, and we showed that digoxin is associated with a higher risk of mortality in these patients. Two other studies investigated specifically the use of digoxin and β-blockers. Fauchier et al. [14] showed that digoxin alone has a neutral impact on survival, similarly to the lack of rate-control treatment, but the addition of a β-blocker significantly improved the outcomes. In their study, treatment with β-blocker alone and digoxin plus β-blocker had a similar positive effect on the outcomes, but their patients had both HF

and AF [14]. Katz et al. [7] reported similar results in a cohort of HF patients, some of whom had AF. We show also that fewer of the patients on digoxin received the guideline-directed treatment, including β-blockers. Our analysis does not allow us to ascertain whether this is due to the worse clinical status of patients (e.g. patients may not tolerate employment or up-titration of HF medication because of low blood pressure or bradycardia) or if the worse clinical status is due to worse quality of treatment.

Our study confirms the findings of Hashim et al. [23] and Ahmed et al. [31] from the Ancillary DIG trial that digoxin does not influence the outcomes of patients with HFpEF.

Possible prescription bias

Digoxin is mostly used in patients with severe HF, and it has been suggested that digoxin might only be a risk marker [24]. Bavendiek et al. [25] argue that the conflicting evidence from numerous studies concerning the use of digoxin suggests a prescription bias, which cannot be entirely ruled out by statistical adjustment for various confounders. Ziff et al. [9] in their meta-analysis showed that the studies with the highest HR for use of digoxin also present the highest risk of bias. Indeed, our analysis shows that the patients on digoxin had a higher mean NYHA class and BNP, a lower mean LVEF, and fewer of them received the guideline-directed treatment. Moreover, the percentage of HF patients receiving digoxin increased with NYHA class, which was shown also in other studies [32]. We showed that HFrEF patients without AF history present the highest HR; however, the harmful effect of digoxin disappears when patients with mild and severe HF are analysed separately.

Our study has several strong points. It analyses the most up-to-date group of patients, chosen to reflect the current ESC guidelines. Our patients were treated with digoxin throughout the follow-up to minimise the bias from unknown duration of treatment, and nearly all of them received the contemporary guideline-directed treatment.

However, we recognise several limitations to our study. This was an observational study, which on one hand allowed us to see a real-life population of patients, but simultaneously did not allow us to rule out hidden bias from unknown confounders. Because this was a registry, the data of some patients were incomplete. Serum digoxin concentrations and the exact doses were not available for analysis. The exact length of treatment with digoxin in patients receiving it prior to inclusion into the ESC Heart Failure Long-Term Registry could not be established.

In conclusion, digoxin is associated with increased risk of death in HFrEF patients without AF history receiving the guideline-directed treatment. Data suggest that digoxin is employed in patients with worse clinical status, which may at least partially explain its association with the increased risk of death. Digoxin has no significant influence on hospitalisation risk in HF patients receiving the guideline-directed treatment.

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