European Review for Medical and Pharmacological Sciences 2023; 27: 7226-7234

The effects of Digoxin use on long-term prognosis in patients with heart failure with reduced ejection fraction

S. OZYILDIRIM[1], H.A. BARMAN[1], O. DOGAN[2], A. ATICI[3], K. MIRZAYEV[1], A.O. EBEOGLU[1], M.T. YUMUK[1], B. IKITIMUR[4], S.M. DOGAN[1], R. ENAR[4]

[1]Department of Cardiology, Istanbul University-Cerrahpaşa, Institute of Cardiology, Istanbul, Turkey
[2]Department of Cardiology, Ministry of Health, Istinye State Hospital, Istanbul, Turkey
[3]Department of Cardiology, Faculty of Medicine, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey
[4]Department of Cardiology, Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey

Abstract. – OBJECTIVE: This study aimed to investigate the effect of digoxin on mortality and rehospitalization in heart failure with reduced ejection fraction (HFrEF) patients. Heart failure is a clinical syndrome that requires frequent rehospitalization and has a high mortality. This study aimed to investigate the effect of digoxin on mortality and rehospitalization in patients with heart failure with reduced ejection fraction.

PATIENTS AND METHODS: The study included 326 patients with HFrEF that were hospitalized for decompensation between September 2014 and January 2016. The patients were divided into two groups: digoxin users and a control group. The study's endpoints were cardiovascular death and rehospitalization after 24-month long-term follow-ups.

RESULTS: Rehospitalization was lower in patients taking digoxin (25% *vs.* 47%, $p = 0.001$). The mean age of patients taking digoxin (n: 78) was 63.7 ± 12.4 years, among which 64% were males. The mean age of the control group was 65.4 ± 11.8 years, among which 74% were males. However, there was no difference in mortality between the two groups (34% *vs.* 45%, $p = 0.10$). While Kaplan-Meier curves revealed no significant differences between mortality rates in the groups (log-rank $p = 0.508$), a statistical difference was found between the groups in rehospitalization rates (log-rank $p = 0.013$). A multiple linear regression analysis revealed that smoking (HR: 1.97, CI: 1.24-3.11, $p = 0.004$), systolic blood pressure (HR: 0.983, CI: 0.974-0.992, $p < 0.001$), atrial fibrillation (HR: 2.09, CI: 1.17-3.72, $p = 0.012$), C-reactive protein (CRP) (HR: 1.009, CI: 1.003-1.015, $p = 0.004$), beta-blockers (HR: 0.891, CI: 0.799-0.972, $p = 0.009$), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (HR: 0.778, CI: 0.641-0.956, $p < 0.001$), mineralocorticoid receptor antagonists (HR: 0.41, CI:0.26-0.65, $p < 0.001$), and digoxin use (HR: 0.59, CI: 0.43-0.80, $p = 0.001$) are independent predictors of rehospitalization in patients with HFrEF.

CONCLUSIONS: Our results show that digoxin use does not affect mortality in HFrEF patients. However, rehospitalization decreased in patients taking digoxin in HFrEF.

Key Words:
Digoxin, Mortality, Rehospitalization, Heart failure.

Introduction

Heart failure (HF) is a significant cause of morbidity and mortality worldwide[1]. Despite significant advances in the treatment of HF, controversy remains regarding some commonly used drugs, including cardiac glycosides. Cardiac glycosides have been used for years because of their positive inotropic effects in HF and negative chronotropic effects in atrial fibrillation (AF). However, observational studies[2,3] published in recent years suggesting that digoxin use may increase mortality have led to a decline in digoxin use. The effect of digoxin in patients with AF and HF with reduced ejection fraction (HFrEF) has not been studied in randomized controlled trials (RCT). Recent studies[4,5] have shown that patients with AF receiving digoxin may have a higher event risk (mortality and rehospitalization). In contrast, non-RCT studies have shown that digoxin does not affect mortali-

Corresponding Author: Omer Dogan, MD; e-mail: omrdgn123@gmail.com

ty in patients with HFrEF and AF[6]. Digoxin can be used in HFrEF to control ventricular rates in patients with high ventricular rate AF[7-9].

Randomized trials examining the effects of digoxin on prognosis in patients with HF are limited and were conducted years ago. The most comprehensive study on this subject was the Digitalis Investigation Group (DIG) study. The DIG study, which examined the use of digoxin in HF, showed that digoxin reduced rehospitalization, whereas no positive effect on mortality was demonstrated. Therefore, the guidelines[3] recommend using digoxin to prevent hospitalization. Digoxin has several indications in the guideline recommendations and is very important in clinical use to reduce morbidity in patients with HF. The use of digoxin in patients with HF did not show a mortality-reducing effect in the DIG study, and other studies in literature have not confirmed this finding. This study aimed to investigate the effect of digoxin on mortality and rehospitalization in HFrEF patients.

Patients and Methods

For this retrospective study, 326 patients with HFrEF [ejection fraction (EF) < 40%, New York Heart Association (NYHA); II-IV] who were hospitalized for decompensation between September 2014 and January 2016 were included. Eighty-two patients were excluded according to the exclusion criteria. In addition to patient demographic characteristics, basal transthoracic echocardiography (TTE), electrocardiogram (ECG), and standard biochemical analyses were recorded, as well as in-hospital and chronic treatments after discharge. Patients with severe end-organ failure during hospitalization, patients with severe noncardiac comorbidities, such as metastatic malignancy and sepsis/septic shock, and patients who died during index hospitalization were excluded from the study (Figure 1).

Patients were divided into two groups: a digoxin user group and a control group. Patients in the digoxin user group whose levels were between 0.8-2.0 ng/ml, which corresponds to the therapeutic range, were included in the study. The study's endpoints were cardiovascular deaths and rehospitalizations after 24-month long-term follow-ups. All patients were over 18 years of age and could provide written informed consent, a prerequisite for enrollment. The study complies with the Declaration of Helsinki, and the Istanbul University-Cerrahpasa Ethics Committee approved the study protocol.

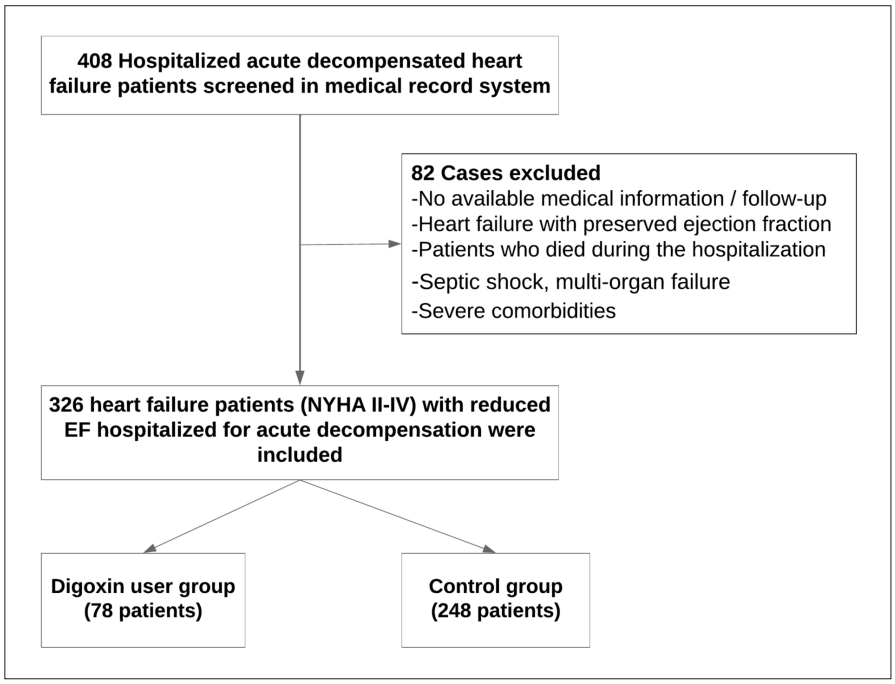

Figure 1. Flowchart of the study.

Echocardiography

Left ventricular EF (LVEF), pulmonary artery systolic pressure (PASP), and mitral regurgitation (MR) were evaluated by TTE according to standard methods and criteria and were accepted as basal findings. TTE studies were performed with a Philips iE33 echocardiography machine and an X5 transducer (Philips Healthcare, Andover, MA, USA) with the patient in the left lateral decubitus position. The left ventricular posterior wall thickness, interventricular septum thickness, left ventricular end-systolic diameter, and left ventricular end-diastolic diameter were measured in all patients. The standard evaluation included M-mode, two-dimensional, and Doppler examinations according to the American Society of Echocardiography (ASE) recommendations[10]. LVEF was calculated from four apical chamber views by manually tracing the end-diastolic and end-systolic endocardial borders according to the Simpson method[11].

Electrocardiography

A 12-lead ECG was recorded at rest in all patients who participated in the study. For these recordings, the filter was 100 Hz, the AC filter was 60 Hz, the paper flow rate was 25 mm/s, and the amplitude was 10 mm/mV. Electrocardiography was performed for the left bundle branch block (LBBB), right bundle branch block, fragmented QRS (fQRS), and AF. The Minnesota criteria to determine LBBB and fQRS require at least two consecutive leads that correspond to areas supplied by the major coronary arteries, notching of the R wave, S wave, RSR' pattern, or multiple R'.

Statistical Analyses

All statistical tests were conducted using the Statistical Package for the Social Sciences 19.0 for Windows (IBM Corp., Armonk, NY, USA). GraphPad Prism 9.5.1 (GraphPad Software, La Jolla, CA, USA) was employed to plot the Kaplan-Meier figures. The Kolmogorov-Smirnov test was used to analyze the normality of the data. Continuous data is expressed as mean ± SD, and categorical data is expressed as percentages. The Chi-square test was used to determine differences between the groups for categorical variables. Student *t*-tests or Mann-Whitney U tests were used as needed to compare unpaired samples. The univariate effects of age, gender, body mass index (BMI), smoking, systolic blood pressure (SBP), NYHA, hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), AF, creatinine, sodium, CRP, LVEF, left atrial (LA) diameter, MR, PASP, beta blocker (BB), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), mineralocorticoid receptor antagonist (MRA), furosemide dose, and digoxin on HF of patients were examined with the log-rank test.

Potential factors identified with univariate analyses were included in the Cox regression analysis with backward selection to determine independent predictors of HF. Only those with clinical significance were included in the correlated factors with similar effects on HF. The proportional hazards assumption and model fit were evaluated using a residual (Schoenfeld and Martingale) analysis. Cumulative survival curves were derived using the Kaplan-Meier method, and differences between curves were analyzed using the log-rank statistic. The significance was assumed at a two-sided $p < 0.05$.

Results

The patients were divided into two groups: digoxin users and a control group. The demographic and clinical characteristics of the study group are shown in Table I. There was no statistically significant difference between the groups regarding age, gender, or BMI. The mean age of patients taking digoxin (n: 78) was 63.7 ± 12.4 years, among which 64% were males, and the mean age of patients in the control group was 65.4 ± 11.8 years, among which 74% were males. There was no statistically significant difference between the groups regarding smoking, HT, DM, and CAD, whereas the frequency of AF was higher in the digoxin user group. SBP was statistically higher in the digoxin user group than in the control group (122.5 ± 24.5 mmHg vs. 115.5 ± 20.2 mmHg; $p = 0.023$). The SBP of 24 (30.8%) patients in the digoxin group and 49 (19.9%) patients in the control group was below 100 mmHg, which was statistically significant. The heart rate of the digoxin user group was lower than that of the control group ($p < 0.001$). In six patients taking digoxin and 58 patients in the control group, the heart rate was above 100/min, and there was a statistically significant difference ($p = 0.002$).

When the NYHA functional capacity was classified as II, III, and IV, a statistically significant difference was found between digoxin users and the control group. The difference was due to patients with a functional capacity between II and

Table I. Baseline characteristics of patients study groups.

	Digoxin user group (n = 78)	Control group (n = 248)	*p*-value
Age (years)	63.7 ± 12.4	65.4 ± 11.8	0.307
Male, n (%)	50 (64%)	175 (70%)	0.282
Body mass index (kg/m^2)	27.8 ± 4.9	28.5 ± 5.9	0.399
Smoker, n (%)	36 (46%)	130 (52%)	0.334
Systolic blood pressure (mmHg)	122.5 ± 24.5	115.5 ± 20.2	0.023
Systolic blood pressure < 100 mmHg, n (%)	24 (30.8%)	49 (19.9%)	0.046
Heart rate/min	75.9 ± 15.4	87.1 ± 15.6	< 0.001
Heart rate > 100/min, n (%)	6 (7.7%)	58 (23.4%)	0.002
NYHA			0.038
class II, n (%)	9 (12%)	54 (22%)	
class III, n (%)	41 (52%)	135 (54%)	
class VI, n (%)	28 (36%)	59 (24%)	
Medical History, n (%)			
Hypertension	45 (57%)	161 (64%)	0.248
Diabetes mellitus	30 (38%)	119 (47%)	0.141
Ischaemic heart disease	37 (47%)	139 (56%)	0.183
Atrial fibrillation	29 (37%)	48 (19%)	0.001
Laboratory Findings			
Hemoglobin (g/dL)	12.2 ± 2.9	12.3 ± 2.1	0.918
Creatinine (mg/dL)	1.17 ± 0.4	1.37 ± 0.5	0.005
Sodium (mEq/L)	134.6 ± 6.1	137.2 ± 4.4	< 0.001
Potassium (mEq/L)	4.3 ± 0.5	4.4 ± 0.7	0.202
Potassium < 3.5 mEq/L, n(%)	4 (5.2%)	22 (8.9)	0.295
Glucose (mg/dl)	112 (89-142)	116 (96-142)	0.340
CRP (mg/L)	12 (4-21)	10 (5-29)	0.780
Albumine (mg/dL)	3.4 ± 0.6	3.5 ± 0.7	0.136
Echocardiographic findings			
Ejection fraction, %	26.0 ± 6.6	27.2 ± 6.3	0.137
Left atrial diameter (mm)	49.4 ± 11.5	44.5 ± 6.5	< 0.001
Mitral regurgitation (3 and 4), n (%)	32 (38%)	84 (34%)	0.633
PASP (mmHg)	47.0 ± 12.5	45.5 ± 13.8	0.455
Treatment			
Beta-blocker, n (%)	59 (75%)	156 (62%)	0.038
ACE-I/ARB, n (%)	56 (71%)	172 (69%)	0.682
MRA, n (%)	40 (51%)	70 (28%)	< 0.001
Furosemid dose (mg/day)	170 (120-300)	240 (120-320)	0.085
Furosemid dose > 100 mg/day, n (%)	67 (85.9%)	223 (90.7%)	0.233
Outcomes, n (%)			
Death	27 (34%)	112 (45%)	0.100
Rehospitalization	20 (25%)	117 (47%)	0.001

IV (p = 0.038). In laboratory tests, hemoglobin, potassium, glucose, C-reactive protein (CRP), and albumin levels were statistically similar between groups, while creatinine (1.17 ± 0.4 mg/dL *vs.* 1.37 ± 0.5mg/dL, p = 0.005) and sodium (134.6 ± 6.1 mEq/L *vs.* 137.2 ± 4.4 mEq/L; p < 0.001) levels were significantly lower in the group taking digoxin. In four patients taking digoxin and 22 patients in the control group, potassium levels were lower than 3.5 mEq/L, and there was no statistical difference (p = 0.295).

There was no statistically significant difference in echocardiographic parameters between EF, MR, and PASP values, but the LA diameter (49.4 ± 11.5 mm *vs.* 44.5 ± 6.5 mm, p < 0.001) was higher in the digoxin user group. BB and ACEI/ARB use rates were similar. MRA use was significantly higher at patient discharge in the digoxin

user group (51% *vs.* 28%; $p < 0.001$). The furosemide dose was higher in the control group but not statistically significant (170 (120-300) mg/day *vs.* 240 (120-320) mg/day, $p = 0.085$). In 67 patients taking digoxin and 253 patients in the control group, the furosemide dose was higher than 100 mg/day, and there was no statistically significant difference ($p = 0.233$).

Cox's proportional hazard regression analysis assessed parameters influencing hospitalization by univariate and multivariate analyses. Age, gender, BMI, smoking, SBP, NYHA, HT, DM, CAD, AF, creatinine, sodium, CRP, LVEF, LA diameter, MR, PASP, BB, ACEI/ARB, spironolactone, furosemide dose, and digoxin parameters were previously assessed with univariate analyses. Univariate analyses revealed statistically significant values, as smoking, SBP, HT, AF, creatinine, CRP, LA diameter, MRA, and digoxin parameters were re-evaluated in multivariate analyses. Smoking, SBP, AF, CRP, BB, ACEI/ARB, MRA, and digoxin were found to be statistically significant independent predictors of rehospitalization (smoking: HR: 1.970, CI: 1.24-3.11, $p = 0.004$; SBP: HR: 0.983, CI: 0.974-0.992, $p < 0.001$; AF: HR: 2.095, CI: 1.17-3.72, $p = 0.012$; CRP: HR: 1.009, CI: 1.003-1.015, $p = 0.004$; BB: HR: 0.891, CI: 0.799-0.972, $p = 0.009$; ACEI/ARB: HR: 0.778, CI: 0.641-0.956, $p < 0.001$; MRA: HR: 0.412, CI: 0.26-0.65, $p < 0.001$; digoxin: HR: 0.590, CI: 0.43-0.80, $p = 0.001$) (Table II).

In addition, the patients taking digoxin and the control group were compared for mortality and rehospitalization after two years of follow-ups. While there were 27 (34%) deaths in the digoxin user group, there were 112 (45%) deaths in the control group. There was no statistical difference between the groups regarding mortality ($p = 0.100$). When comparing rehospitalization rates, rehospitalization was observed in 20 (25%) patients using digoxin, while 117 (47%) patients were rehospitalized in the control group. A significant reduction in rehospitalization was observed in patients taking digoxin ($p = 0.001$).

When comparing differences in event-free survival in the entire study population as a function of digoxin use, the cumulative incidence of all-cause mortality at two years of follow-up, survival rates were assessed using Kaplan-Meier curves, and there was no statistically significant difference (log-rank $p = 0.508$; Figure 2). Rehospitalization rates were statistically significantly different between the two groups (log-rank $p = 0.013$; Figure 3).

Discussion

This study investigated the prognostic significance of digoxin use in patients with HFrEF. The following were the main findings of our study: (i) patients taking digoxin had lower rehospitalization rates than those not taking digoxin; (ii) Kaplan-Meier curves revealed no significant difference between mortality rates in the groups, but a statistical difference was found between the groups in rehospitalization rates; (iii) multivariate analyses revealed that smoking, AF, CRP, MRA, and digoxin were independent predictors of rehospitalization in patients with HFrEF.

HF is a significant cause of morbidity and mortality worldwide1. Evidence-based pharmacological therapies [renin-angiotensin-aldosterone system (RAAS) blockers/angiotensin receptor neprilysin inhibitors (ARNI), BBs, MRA, ivabradine, and combination therapies] that significantly reduce mortality in patients with HFrEF are not available in all patients because of noncardiac comorbidities such as renal dysfunction and advanced age. The low frequency of the use of electrical therapies [such as cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD)] and left ventricular assist devices has limited the treatment of HF. Despite advances in diagnosis and treatment, the prognosis of HF is worse than that of most malignancies[2].

Digoxin is the most commonly used cardiac glycoside. It is absorbed from the intestine, passed into the blood, and distributed to all tissues, including the central nervous system. Digoxin inhibits the Na/K-ATPase enzyme (sodium pump) and has a positive inotropic effect[12]. Digoxin is recommended in guidelines for symptomatic HFrEF patients despite treatment with RAAS blockers/ARNI, BBs, diuretics, and MRA when indicated. Therefore, studies performed on digoxin reflect past data and data on current clinical use is insufficient. Previous studies[13,14] have shown that digoxin is not used in enough patients, as recommended by the guidelines.

There is no randomized evidence of the efficacy of digoxin as an adjunctive therapy in HF. This is because most landmark drug trials in the modern treatment of HF were published after randomized trials of digoxin[15]. DIG[3], which studied the use of digoxin in patients with sinus rhythm and HFrEF, randomized patients to a placebo or digoxin group in addition to

Table II. Univariate and multivariate Cox's proportional Hazard regression Analysis of Predictors of Cardiovascular Rehospitalization in Heart Failure Patients.

Variable	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.995	0.981-1.009	0.460			
Gender	1.304	0.906-1.878	0.153			
Body mass index	0.983	0.954-1.013	0.266			
Smoking	2.345	1.366-4.026	0.002	1.970	1.244-3.118	0.004
Systolic blood pressure (mmHg)	0.985	0.974-0.997	0.013	0.983	0.974-0.992	< 0.001
NYHA			0.250			
Hypertension	1.383	0.984-1.945	0.062	1.334	0.783-2273	0.289
Diabetes mellitus	0.987	0.704-1.385	0.941			
Ischaemic heart disease	1.057	0.754-1.482	0.748			
Atrial fibrillation	2.028	1.042-3.944	0.037	2.095	1.179-3.721	0.012
Creatinine	1.529	1.162-2.011	0.002	1.360	0.971-1.904	0.074
Sodium	0.990	0.957-1.025	0.587			
C-reactive protein	1.010	1.003-1.017	0.005	1.009	1.003-1.015	0.004
Ejection fraction	0.362	0.027-4.810	0.442			
Left atrial diameter	1.121	1.024-2.217	0.042	1.257	0.875-3.584	0.342
Mitral regurgitation	0.999	0.843-1.184	0.995			
Pulmonary artery systolic pressure	1.001	0.985-1.017	0.903			
Beta-blocker	0.885	0.783-0.959	< 0.001	0.891	0.799-0.972	0.009
ACE-I/ARB	0.726	0.551-0.926	< 0.001	0.778	0.641-0.956	< 0.001
MRA	0.405	0.236-0.697	0.001	0.412	0.261-0.652	< 0.001
Furosemide dose	1.000	0.999-1.001	0.854			
Digoxin	0.340	0.169-0.683	0.002	0.590	0.434-0.803	0.001

NYHA, New York Heart Association; CRP, C-reactive protein; PASP, pulmonary artery systolic pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; MRA, mineralocorticoid receptor antagonist.

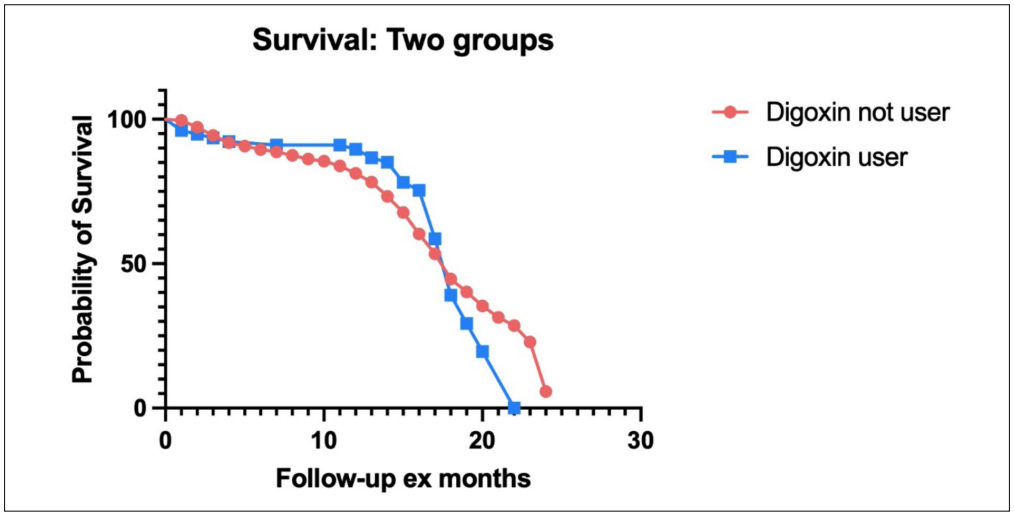

Figure 2. Comparison of Kaplan-Meier curve for death between digoxin users and control group ($p = 0.508$; log-rank test).

a diuretic and angiotensin-converting enzyme inhibitor (ACE-I). In this study, no positive effect of digoxin on mortality was observed. However, in patients hospitalized for HF, a relative risk reduction of 28% was achieved within an average of three years after the initiation of digoxin treatment.

In the studies PROVED[16] and RADIANCE[17], published around the same time, HF worsening was observed after discontinuation of digoxin

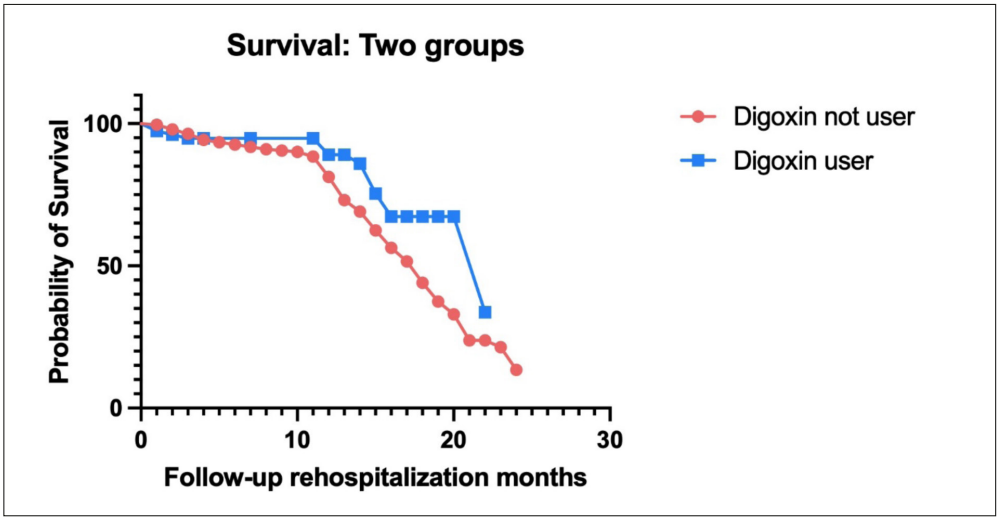

Figure 3. Comparison of Kaplan-Meier curve for rehospitalization between digoxin users and control group (p = 0.013; log-rank test).

therapy. The ancillary DIG study[18] in 988 HF patients with normal sinus rhythms and preserved systolic functions (LVEF > 45%) showed no effect of digoxin therapy on mortality. In a study of 4,467 patients published in 2011, Andrey et al[19] found that digoxin therapy was associated with improved mortality and morbidity of HF, including in women and patients with non-systolic HF. In a meta-analysis of 52 studies published in 2015, Ziff et al[6] found that using digoxin in HF was ineffective on mortality in randomized trials and was associated with a low hospitalization rate in all study types. Adams et al[20] reported that digoxin at effective serum concentrations reduced the risk of hospitalization and increased exercise capacity in patients with HF. In the study published by Georgiopoulou et al[21], digoxin treatment was ineffective in terms of mortality in 455 patients with advanced HF. In 2017, Lopes et al[22] found that digoxin use was associated with higher mortality, independent of HF. In our study, we found that digoxin was used with indications consistent with current guidelines, and 37% of patients taking digoxin had AF. In most of the patients included in our study, we found that it was used to control heart rate or HF symptoms in patients with AF and the functional capacity of NYHA III-IV. We found that digoxin use had no effect on HF mortality, but it reduced hospitalizations.

Limitations

The study's major limitation was the small number of patients and the single-centered study. Another limitation of the study is that it did not provide data on whether patients received device (ICD, CRT) therapy. Since ARNI treatment is not covered by health insurance in our country, patients taking ARNI are not included.

Conclusions

Digoxin may have late-onset favorable effects on the cardiovascular rehospitalization of class II-IV, EF < 40% HF, who already receive a triple combination of RAAS blockers, BB, and MRA. These effects tend to add up over time, just as with RAAS inhibitors – a finding that must be considered during follow-up. Further prospective studies are needed to determine the effect of digoxin use on the prognosis in HF patients with reduced EF.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

The Internal Review Board approved the study protocol at the Istanbul University-Cerrahpasa Ethics Committee (Protocol number: 21.10.2022-514260).

Funding
The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Authors' Contributions
All authors contributed to one or more of the following steps; the design of the study, data acquisition, or analysis and interpretation of data, drafting or revising the article and final approval of the manuscript to be published.

Data Availability
The datasets of the current study are available upon reasonable request.

References

1) Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2012; 347: 1397-1402.
2) Piotr P, Adriaan AV, Stefan DA, Héctor B, John GFC, Andrew JSC, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200.
3) Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336: 525-533.
4) Ouyang AJ, Lv YN, Zhong HL, Wen JH, Wei XH, Peng HW, Zhou J, Liu LL. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. Am J Cardiol 2015; 115: 901-906.
5) Vamos M , Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. Eur Heart J 2015; 36: 1831-1838.
6) Ziff OJ , Lane DA, Samra M, Griffith M, Kirchhof P, Lip GYH, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015; 351: h4451.
7) Van Gelder IC , Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Veldhuisen DJV, den Berg MPV, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010; 362: 1363-1373.
8) Bavishi C, Khan AR, Ather S. Digoxin in patients with atrial fibrillation and heart failure: a meta-analysis. Int J Cardiol 2015; 188: 99-101.
9) Freeman JV , Reynolds K, Fang M, Udaltsova N, Steimle A, Pomernacki NK, Borowsky LH, Harrison TN, Singer DE, Go AS. Digoxin and risk of death in adults with atrial fibrillation: the ATRIA-CVRN Study. Circ Arrhythm Electrophysiol 2015; 8: 49-58.
10) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L,Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 233-271.
11) Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman NH, Brundage B, Botvinick EH, Boswell R, Carlsson E, Parmley WW. Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation 1979; 60: 547-555.
12) Tintinalli JE, Stapczynski JS, Ma OJ, Yealy DM, Meckler GD, Cline DM. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, seventh edition, McGraw Hill 2016; 1260-1264.
13) Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation 2010; 122: 585-596.
14) Jaarsma T, Årestedt KF, Mårtensson J, Dracup K, Strömberg A. The European Heart Failure Self-care Behaviour scale revised into a nine-item scale (EHFScB-9): a reliable and valid international instrument. Eur J Heart Fail 2009; 11: 99-105.
15) Chaggar PS, Steven MS, Simon GW. "Is foxglove effective in heart failure?." Cardiovasc Ther 2015; 33: 236-241.
16) Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. J Am Coll Cardiol 1993; 22: 955-962.
17) O'Mara NB, Zimmerman WB. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993; 329: 1819-1820.
18) Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006; 114: 397-403.

19) Andrey JL, Romero S, García-Egido A, Escobar MA, Corzo R, Garcia-Dominguez G, Lechuga V, Gómez F. "Mortality and morbidity of heart failure treated with digoxin. A propensity-matched study." Int J Clin Pract 2011; 65: 1250-1258.

20) Adams JKF, Ghali JK, Herbert PJ, Stough WG, Butler J, Bauman JL, Ventura HO, Sabbah H, Mackowiak JI, Veldhuisen DJV. A perspective on re-evaluating digoxin's role in the current management of patients with chronic systolic heart failure: targeting serum concentration to reduce hospitalization and improve safety profile. Eur J Heart Fail 2014; 16: 483-493.

21) Georgiopoulou VV, Kalogeropoulos AP, Giamouzis G, Agha SA, Rashad MA, Waheed S, Laskar S, Smith AL, Butler J. Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. Circ Heart Fail 2009; 2: 90-97.

22) Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, Ridefelt P, Lawrence JH, Caterina RD, Vinereanu D, Hanna M, Flaker G, Al-Khatib SM, Hohnloser SH, Alexander JH, Granger CB, Wallentin L; ARISTOTLE Committees and Investigators. Digoxin and mortality in patients with atrial fibrillation. J Am Coll Cardiol 2018; 71: 1063-1074.