Digitalis Therapy and Risk of Recurrent Ventricular Tachyarrhythmias and ICD Therapies in Atrial Fibrillation and Heart Failure

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Keywords

Ventricular tachycardia · Ventricular fibrillation · Mortality · Digitalis · Heart failure · Atrial fibrillation · Implantable cardioverter defibrillator · Medical treatment · Pharmacological drugs

Abstract

Objective: This study sought to assess the impact of treatment with digitalis on recurrences of ventricular tachyarrhythmias in implantable cardioverter defibrillator (ICD) recipients with atrial fibrillation (AF) and heart failure (HF). **Background:** The data regarding outcomes of digitalis therapy in ICD recipients are limited. **Methods:** A large retrospective registry was used, including consecutive ICD recipients with episodes of ventricular tachyarrhythmia between 2002 and 2016. Patients treated with digitalis were compared to patients without digitalis treatment. The primary prognostic outcome was first recurrence of ventricular tachyarrhythmia

at 5 years. Kaplan-Meier and multivariable Cox regression analyses were applied. **Results:** A total of 394 ICD recipients with AF and/or HF was included (26% with digitalis treatment and 74% without). Digitalis treatment was associated with decreased freedom from recurrent ventricular tachyarrhythmias (HR = 1.423; 95% CI 1.047–1.934; $p = 0.023$). Accordingly, digitalis treatment was associated with decreased freedom from appropriate ICD therapies (HR = 1.622; 95% CI 1.166–2.256; $p = 0.004$) and, moreover, higher rates of rehospitalization (38 vs. 21%; $p = 0.001$) and all-cause mortality (33 vs. 20%; $p = 0.011$). **Conclusion:** Among ICD recipients suffering from AF and HF, treatment with digitalis was associated with increased rates of recurrent ventricular tachyarrhythmias and ICD therapies. However, the endpoints may also have been driven by interactions between digitalis, AF, and HF.

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Introduction

Treatment with an implantable cardioverter defibrillator (ICD) is the therapeutic cornerstone of effective primary and secondary prevention of ventricular tachyarrhythmias and sudden cardiac death (SCD). ICDs have been shown to effectively decrease long-term mortality among patients suffering from cardiovascular diseases [1–3]. Additionally, optimal pharmacotherapy is recommended in order to ensure optimal long-term survival, especially with heart failure (HF) or multimorbid disease syndromes [4, 5].

The most common risk factor for the development of ventricular tachyarrhythmias is coronary artery disease, in more than 80% of affected patients [6]. Furthermore, the presence of atrial fibrillation (AF) has recently been shown to increase the risk of ventricular tachyarrhythmias and SCD [7–9]. The higher risk of ventricular tachyarrhythmias with AF may be attributed to an increasing burden of comorbidities including coronary artery disease and cardiomyopathies, or to higher rates of short-long-short cycles degenerating into ventricular tachyarrhythmias [9]. HF itself represents another independent risk factor for recurrent ventricular tachyarrhythmias, especially in ICD recipients for primary prevention [10]. Both AF and HF may be treated pharmacologically with cardiac glycosides in order to prevent recurrent episodes of supraventricular tachycardia and to potentially improve cardiac inotropy and HF-related symptoms [11, 12].

Whether there is a beneficial prognostic effect related to digitalis therapy is still under ongoing debate. Researchers question any effective reduction in rehospitalizations due to HF [13, 14] and mortality benefits for AF patients [15] and debate the heterogeneous results for long-term mortality among HF patients [13, 16]. Accordingly, digitalis is no longer recommended as HF treatment, with prescriptions for this indication decreasing [17]. In contrast, the prospective randomized DIGIT-HF trial (EudraCT No. 2013-005326-38) currently reevaluates the prognostic impact of digitalis on systolic HF [17]. However, even fewer studies focused on the impact of digitalis on ICD-related therapies [18–20].

Notably, there are no data with regard to whether digitalis affects recurrence of ventricular tachyarrhythmias in patients with a prior history of ventricular tachyarrhythmias. Therefore, this study evaluates the prognostic impact of digitalis therapy on the primary endpoint of recurrence of ventricular tachyarrhyth-

mias, as well as on secondary endpoints (i.e., appropriate ICD therapies, rehospitalization, and all-cause mortality), in ICD recipients with HF, AF, and beta-blocker therapy surviving episodes of ventricular tachyarrhythmia.

Subjects and Methods

Data Collection and Documentation

The present study retrospectively included all consecutive ICD recipients surviving index episodes of ventricular tachyarrhythmia on admission between 2002 and 2016 at our institution. All relevant clinical data related to the index event, as well as those related to recurrences of ventricular tachyarrhythmias and rehospitalizations, were documented using the patients' files, daily records, documentation from diagnostic examinations and laboratory values, electrocardiograms (ECG), device recordings, and all further information derived from the electronic hospital information system.

Ventricular tachyarrhythmias comprised ventricular tachycardia (VT) and ventricular fibrillation (VF), as defined by current international guidelines [4, 21]. Sustained VT was defined by a duration >30 s or causing hemodynamic collapse within 30 s, nonsustained VT by a duration <30 s both with a wide QRS complex (≥ 120 ms) at a rate >100 bpm [4]. Ventricular tachyarrhythmia at index was documented by 12-lead ECG, ECG telemonitoring, ICD, or, in case of an unstable course or during resuscitation, by external defibrillator monitoring. Documented VF was treated by ICD-related shock or external defibrillation, and in case of prolonged instability, with additional intravenous antiarrhythmic drugs during cardiopulmonary resuscitation. Electrical storm was defined as ≥ 3 episodes of ventricular tachyarrhythmia requiring appropriate device therapy and occurring during a period of 24 h [4, 22].

Further documented data contained baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, and data derived from all noninvasive or invasive cardiac diagnostics and device therapies. These included coronary angiography, electrophysiological examination, and prior or newly implanted ICDs, pacemakers or cardiac contractility modulators which had already been implanted at index or at follow-up. Imaging modalities comprised echocardiography and cardiac magnetic resonance imaging.

The following device types were allowed: ICD, cardiac resynchronization therapy with defibrillator (CRT-D), and subcutaneous ICD. ICD recipients routinely presented to our clinic every 3–6 months for device check, as well as unscheduled in case of noticed device interrogations. Device setting and programming were performed according to current international guidelines by cardiologists specialized in electrophysiology during routine clinical care [4, 21, 23]. The device recordings were reevaluated retrospectively by independent cardiologists being blinded to the final data analysis.

The present study is derived from an analysis of the Registry of Malignant Arrhythmias and Sudden Cardiac Death – Influence of Diagnostics and Interventions (RACE-IT), a single-center registry including consecutive patients presenting with ventricular tachyarrhythmia and SCD being acutely admitted to the University Medical Center Mannheim (UMM), Germany (ClinicalTrials.gov identifier: NCT02982473), between 2002 and 2016.

Inclusion and Exclusion Criteria

Consecutive ICD recipients with HF, AF, and beta-blocker therapy were included. All patients had a documented episode of ventricular tachyarrhythmia, which defines the index event. All patients analyzed had to survive index hospitalization and were discharged with documented beta-blocker therapy. HF was defined as a documented left ventricular ejection fraction (LVEF) <45% [11]. Paroxysmal AF was defined as self-terminating in most cases within 48 h and, lately, for ≤ 7 days, including AF episodes that are cardioverted within 7 days. Persistent AF lasts >7 days, including episodes terminated by cardioversion either with drugs or by direct current cardioversion after ≥ 7 days. Permanent AF was defined as accepted by the patient and physician without pursuing further rhythm control. AF patients may have all degrees of LVEF [12].

The decision to treat patients with beta-blockers and digitalis was based on the discretion of the cardiologists during routine care according to European guidelines [4, 11, 12, 21]. Patients without an activated ICD, HF, AF, beta-blocker treatment, or death at index hospitalization were excluded from the present analysis. To guarantee sufficient documentation of recurrent ventricular tachyarrhythmias, patients not presenting for at least one ICD check during follow-up were excluded from the present study.

Definition of the Case and Control Groups

The case group (digitalis group) comprised all patients with digitalis and beta-blocker treatment at discharge. Both digoxin and digitoxin were allowed. The control group (non-digitalis group) comprised all patients with beta-blocker but no digitalis treatment at discharge. All other medical therapies apart from beta-blockers and digitalis were allowed.

Primary and Secondary Endpoints

Follow-up period was set at 5 years for all outcomes. The primary prognostic endpoint was the first recurrence of ventricular tachyarrhythmia (VT or VF) as documented within the ICD protocols. Secondary endpoints were overall recurrences at follow-up, recurrences per patient, associated appropriate or inappropriate device therapies (first, overall, and per patient), first rehospitalization, and all-cause mortality at follow-up. Further stratification into subgroups of primary or secondary prevention and appropriate or inappropriate device therapies was performed.

Appropriate device therapy was defined as device-related therapy in the presence of VT or VF, including antitachycardia pacing (ATP), ICD shock, or both ATP and shock. Inappropriate device therapy was defined as ATP or ICD shock in the absence of VT or VF. First rehospitalizations comprised rehospitalizations due to VT, VF, acute myocardial infarction, acute HF, and inappropriate device therapy.

All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices (bureau of mortality statistics) all across Germany. Identification of patients was verified by name, surname, day of birth, and registered living address.

Statistical Methods

Quantitative data are presented as mean $\pm$ standard error of mean (SEM), median and interquartile range (IQR), and range depending on the distribution of the data, and they were compared using the Student *t* test for normally distributed data or the Mann-Whitney U test for nonparametric data. Deviations from a Gauss-

Table 1. Distribution and dosages of digitalis and BB

	No digitalis (n = 290; 74%)		Digitalis (n = 104; 26%)		p value (distribution/ dosage)
	Subjects, n (%)	Dosage, mg/day	Subjects, n (%)	Dosage, mg/day	
Digoxin	–	–	71 (68)	0.14 $\pm$ 0.007	–
Digitoxin	–	–	33 (32)	0.08 $\pm$ 0.003	–
Metoprolol	168 (58)	80.6 $\pm$ 3.1	43 (41)	73.4 $\pm$ 4.7	0.004 /0.279
Carvedilol	72 (25)	19.5 $\pm$ 1.6	39 (38)	20.6 $\pm$ 2.5	0.014 /0.706
Bisoprolol	33 (11)	5.8 $\pm$ 0.5	10 (10)	5.0 $\pm$ 1.0	0.693/0.470
Other type of BB	17 (6)		12 (12)		0.057

Dosages are given as mean $\pm$ SEM. Bold denotes significance. BB, beta-blocker.

ian distribution were tested by the Kolmogorov-Smirnov test. Spearman's rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies, and compared using the χ^2 test or the Fisher exact test, as appropriate.

Firstly, the univariable Kaplan-Meier method was applied to evaluate prognostic differences within the entire cohort, between the subgroups of primary and secondary prevention, and between the subgroups of appropriate and inappropriate ICD therapies, each stratified according to digitalis and non-digitalis therapy. Then, the impact of digitalis was analyzed separately for AF and HF, allowing the combination of AF and HF. Finally, the subgroups of "AF only" (AF patients without HF) and "HF only" (HF patients without AF) were analyzed. Hazard ratios (HRs) are given together with 95% confidence intervals (CIs).

Secondly, multivariable Cox regression models were developed using the "forward selection" option, where only statistically significant variables ($p < 0.05$) were included and analyzed simultaneously. Predefined variables being used for multivariable Cox regressions included: baseline parameters (age, gender), chronic diseases (chronic kidney disease, diabetes mellitus), the combination of AF and HF, and digitalis therapy. Patients without complete follow-up were censored (accepted lost-to-follow-up rate: <10%).

The result of a statistical test was considered significant with $p < 0.05$, a statistical trend was defined as $p < 0.10$. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS (version 25; IBM, Armonk, NY, USA) were used for statistical analysis.

Results

Study Population

A total of 394 consecutive ICD recipients with HF (87%) and/or AF (44%), of which 31% revealed both entities, was included. All patients survived an index episode of ventricular tachyarrhythmia and were discharged with

Table 2. Baseline characteristics and comorbidities

Characteristic	Non-digitalis (<i>n</i> = 290; 74%)	Digitalis (<i>n</i> = 104; 26%)	<i>p</i> value
Median age (range), years	66 (32–87)	68 (32–80)	0.143
Male gender, <i>n</i> (%)	239 (82)	83 (80)	0.555
Ventricular tachyarrhythmia at index, <i>n</i> (%)			0.588
Ventricular tachycardia	224 (77)	83 (80)	
Ventricular fibrillation	66 (23)	21 (20)	
Cardiovascular risk factors, <i>n</i> (%)			
Arterial hypertension	193 (67)	71 (68)	0.749
Diabetes mellitus	76 (26)	33 (32)	0.280
Hyperlipidemia	130 (45)	50 (48)	0.568
Smoking	91 (31)	27 (26)	0.301
Cardiac family history	41 (14)	16 (15)	0.757
Comorbidities at index stay, <i>n</i> (%)			
Heart failure	252 (87)	91 (88)	0.875
Atrial fibrillation	113 (39)	59 (57)	0.002
Paroxysmal	76 (26)	41 (39)	
Persistent	14 (5)	6 (6)	0.018
Permanent	23 (8)	12 (12)	
Coronary artery disease	225 (78)	71 (68)	0.059
Cardiogenic shock	22 (8)	11 (11)	0.345
CPR	55 (19)	14 (14)	0.333
Chronic kidney disease	129 (45)	49 (48)	0.627
Medication at discharge, <i>n</i> (%)			
Beta-blocker	290 (100)	104 (100)	1.000
ACE inhibitor	221 (76)	75 (72)	0.408
ARB	31 (11)	20 (19)	0.030
Aldosterone antagonist	53 (18)	27 (26)	0.095
Amiodarone	70 (24)	20 (19)	0.306
Mean ECG intervals ± SD			
PQ	173±5	190±9	0.079
QRS	117±5	109±8	0.391
QT	415±5	401±7	0.138
LVEF, <i>n</i> (%)			0.162
≥55%	18 (6)	5 (5)	
54–45%	11 (4)	1 (1)	
44–35%	79 (28)	20 (21)	
<35%	173 (62)	71 (73)	
Not documented	9 (–)	7 (–)	

Bold denotes significance. CPR, cardiopulmonary resuscitation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; LVEF, left ventricular ejection fraction.

or without digitalis treatment (non-digitalis 74% vs. digitalis 26%; $p = 0.0001$). The target dosages were reached already at discharge, as seen for digoxin in 68% (mean dosage 0.14 mg/day) and for digitoxin in 32% (mean dosage 0.08 mg/day). Furthermore, the most commonly administered beta-blocker was metoprolol, with the target dosages being reached at discharge already (Table 1).

As seen in Table 2, the median age was 67 years, and most patients were of male gender (81%). VT was more

common than VF (77–80 vs. 20–23%) at index in both treatment groups. The rates of VT and VF were comparable between the digitalis and the non-digitalis patients (VT: 77–80%; VF: 20–23%). The overall rates of HF were comparable between the digitalis and the non-digitalis group (88 vs. 87%), whereas significantly more digitalis patients suffered from AF (57 vs. 39%) with or without HF. The percentage of these patients with both entities was 26% (non-digitalis) and 44% (digitalis), re-

Table 3. Baseline characteristics and comorbidities stratified by atrial fibrillation and heart failure

Characteristic	Atrial fibrillation			Heart failure		
	non-digitalis (<i>n</i> = 113; 66%)	digitalis (<i>n</i> = 59; 34%)	<i>p</i> value	non-digitalis (<i>n</i> = 252; 73%)	digitalis (<i>n</i> = 91; 27%)	<i>p</i> value
Median age (range), years	70 (32–87)	68 (45–80)	0.717	66 (22–87)	68 (32–82)	0.079
Male gender, <i>n</i> (%)	93 (82)	48 (81)	0.878	208 (83)	74 (81)	0.794
Ventricular tachyarrhythmia at index, <i>n</i> (%)			0.301			0.741
Ventricular tachycardia	84 (74)	48 (81)		198 (79)	73 (80)	
Ventricular fibrillation	29 (26)	11 (19)		54 (21)	18 (20)	
Cardiovascular risk factors, <i>n</i> (%)						
Arterial hypertension	78 (69)	43 (73)	0.599	164 (65)	62 (68)	0.599
Diabetes mellitus	28 (25)	20 (34)	0.206	66 (26)	26 (29)	0.660
Hyperlipidemia	49 (43)	31 (53)	0.252	114 (45)	45 (50)	0.490
Smoking	29 (26)	15 (25)	0.973	83 (33)	21 (23)	0.079
Cardiac family history	13 (12)	12 (20)	0.119	37 (15)	14 (15)	0.872
Comorbidities at index stay, <i>n</i> (%)						
Heart failure	75 (66)	46 (78)	0.114	252 (100)	91 (100)	1.000
Atrial fibrillation	113 (100)	59 (100)	1.000	75 (30)	46 (51)	0.001
Paroxysmal	76 (68)	41 (70)		50 (20)	30 (33)	
Persistent	14 (12)	6 (10)	0.908	10 (4)	5 (6)	0.004
Permanent	23 (20)	12 (20)		15 (6)	11 (12)	
Coronary artery disease	86 (76)	38 (64)	0.104	200 (79)	63 (69)	0.050
Cardiogenic shock	8 (7)	8 (14)	0.165	20 (8)	9 (10)	0.566
CPR	21 (19)	10 (17)	0.791	46 (18)	11 (12)	0.176
Chronic kidney disease	55 (49)	27 (46)	0.717	115 (46)	43 (48)	0.772
Medication at discharge, <i>n</i> (%)						
Beta-blocker	113 (100)	59 (100)	1.000	252 (100)	91 (100)	1.000
ACE inhibitor	83 (74)	40 (68)	0.435	195 (77)	67 (74)	0.470
ARB	11 (10)	12 (21)	0.055	27 (11)	19 (21)	0.017
Aldosterone antagonist	25 (22)	17 (29)	0.332	50 (20)	24 (26)	0.194
Amiodarone	40 (35)	10 (17)	0.011	63 (25)	19 (21)	0.430
Mean ECG intervals ± SEM						
PQ	159±3	170±10	0.249	173±5	192±10	0.062
QRS	114±7	109±10	0.668	117±5	108±8	0.361
QT	416±7	400±0	0.112	414±5	401±7	0.183
LVEF, <i>n</i> (%)			0.113			0.091
≥55%	18 (17)	5 (10)		– (–)	– (–)	
54–45%	11 (11)	1 (2)		– (–)	– (–)	
44–35%	17 (16)	10 (19)		79 (31)	20 (22)	
<35%	58 (56)	36 (69)		173 (69)	71 (78)	
Not documented	9 (–)	7 (–)	–	– (–)	– (–)	–

ECG intervals are given as mean ± SEM. Bold denotes significance. CPR, cardiopulmonary resuscitation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; LVEF, left ventricular ejection fraction.

spectively. Despite a slightly higher rate of angiotensin receptor blocker use in the digitalis group, no further significant differences were observed between the two groups, especially regarding rates of cardiogenic shock, cardiopulmonary resuscitation, and chronic kidney disease. Especially ECG intervals, coronary artery disease rates, and the LVEF were similar in both groups (Table 1).

Table 3 presents the characteristics of patients with AF (left columns) and HF (right columns). Among the AF patients, comorbidities and LVEF groups were equally distributed. However, a higher rate of amiodarone treatment was seen for those patients not on digitalis. Among the HF patients, AF was more common in the digitalis group than in the non-digitalis patients, with a higher rate of angiotensin receptor blocker treatment.

Fig. 1. Freedom from first recurrence of ventricular tachyarrhythmia (overall, left panel), stratified by primary (middle panel) and secondary preventive implantable cardioverter defibrillator recipients (right panel). VT, ventricular tachycardia; VF, ventricular fibrillation.

Fig. 2. Digitalis treatment decreased freedom from appropriate device therapy (left panel), but it did not affect freedom from inappropriate device therapy (right panel).

Table 4 outlines the ICD-related data for the study population. Most patients had an activated transvenous ICD (88–93%), whereas a minority of the patients had a transvenous CRT-D or subcutaneous ICD (1–10%). The ICD was mostly implanted for secondary prevention (55 vs. 45%). The median detection thresholds for VT (171 vs. 176 bpm) and for VF (214 bpm) were comparable between the two groups, as well as was the median cycle length of VT, ranging from 315 to 320 ms (Table 4).

Follow-Up Data and Primary and Secondary Endpoints

At least 90% of the patients were followed up regularly within the follow-up period of 5 years (1,825 days) with ≥ 1 ICD check-up every 6–12 months.

Freedom from first episodes of ventricular tachyarrhythmia was decreased in digitalis patients (59 vs. 43%; log-rank $p = 0.023$; HR = 1.423; 95% CI 1.047–1.934; $p = 0.023$) (Table 4; Fig. 1, left panel). Notably, this difference was mainly observed among patients with secondary preventive ICDs (68 vs. 43%; log-rank $p = 0.004$; HR = 1.776; 95% CI 1.196–2.638; $p = 0.004$), but not in primary preventive ICD recipients (log-rank $p = 0.835$) (Fig. 1, middle and right panels). The increasing rates of first recurrence were mainly attributable to sustained VT (43 vs. 25%), which was also reflected in an increasing rate of overall sustained VT (53 vs. 31%) (Table 4).

Freedom from first appropriate device therapy was decreased in digitalis patients (53 vs. 34%; log-rank $p = 0.004$; HR = 1.622; 95% CI 1.166–2.256; $p = 0.004$) (Fig. 2, left

Table 4. ICD data and primary and secondary endpoints

Characteristic	Non-digitalis (n = 290; 74%)	Digitalis (n = 104; 26%)	p value
Type of ICD, n (%)			0.304
ICD	255 (88)	97 (93)	
CRT-D	28 (10)	6 (6)	
s-ICD	7 (2)	1 (1)	
Implant indication, n (%)			0.859
Primary prevention	134 (46)	47 (45)	
Secondary prevention	156 (54)	57 (55)	
ICD programming, bpm ¹			
VT detection threshold	171 (167–171)	176 (167–176)	0.073
VF detection threshold	214 (214–217)	214 (214–222)	0.078
<i>Primary endpoint</i>			
First recurrence of ventricular tachyarrhythmia, n (%)			
Overall	124 (43)	61 (59)	0.006
Nonsustained VT	33 (11)	9 (9)	0.440
Sustained VT	73 (25)	45 (43)	0.001
VF	18 (6)	7 (7)	0.570
Electrical storm	18 (6)	11 (11)	0.143
<i>Secondary endpoints</i>			
Overall recurrences at follow-up, n (%)			
Nonsustained VT	53 (18)	19 (18)	0.999
Sustained VT	90 (31)	55 (53)	0.001
VF	28 (10)	14 (14)	0.281
Electrical storm	18 (6)	11 (11)	0.143
VT cycle length, ms ¹	315 (280–345)	320 (300–350)	0.444
Recurrences per patient ²			
Nonsustained VT	5.3±2.3	8.4±4.8	0.523
Sustained VT	5.3±1.3	9.2±3.6	0.198
VF	0.3±0.1	0.4±0.2	0.604
Electrical storm	0.1±0.0	0.1±0.0	0.144
First device therapies, n (%)			
Overall appropriate device therapy	98 (34)	55 (53)	0.001
Appropriate shock	38 (13)	19 (18)	0.199
Appropriate ATP only	53 (18)	32 (31)	0.007
Inappropriate device therapy	36 (13)	16 (15)	0.450
Overall device therapies at follow-up, n (%)			
Overall appropriate device therapy	98 (34)	55 (53)	0.001
Appropriate shock	57 (20)	20 (29)	0.055
Appropriate ATP only	80 (28)	44 (42)	0.006
Inappropriate device therapy	36 (13)	16 (15)	0.450
Device therapies per patient ²			
Appropriate shock	0.5±0.1	1.5±0.5	0.003
Appropriate ATP only	4.4±1.1	7.3±3.5	0.283
Inappropriate device therapy	0.4±0.1	0.4±0.1	0.608
First rehospitalization, n (%)			
Overall	61 (21)	39 (38)	0.001
VT	24 (8)	17 (16)	0.021
VF	5 (2)	1 (1)	1.000
AMI	5 (2)	1 (1)	1.000
Acute heart failure	16 (6)	14 (13)	0.009
Inappropriate device therapy	11 (4)	6 (6)	0.395
All-cause mortality at 5 years, n (%)	59 (20)	34 (33)	0.011

Bold denotes significance. ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator; s-ICD, subcutaneous ICD; AMI, acute myocardial infarction; ATP, antitachycardia pacing; HF, heart failure; VF, ventricular fibrillation; VT, ventricular tachycardia. ¹ Median (IQR). ² Mean ± SEM.

Fig. 3. a AF patients. Digitalis therapy was still associated with a trend for an increased risk of recurrent VT/VF (left) and appropriate ICD therapy (right) in the subgroup of AF patients. **b** HF patients. Digitalis therapy was not associated with an increased risk of recurrent VT/VF (left), but with an increased risk of appropriate ICD therapy (right) in the subgroup of HF patients. AF, atrial fibrillation; HF, heart failure; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator.

panel), whereas no difference was found for inappropriate device therapies (Fig. 2, right panel). The differences in first appropriate therapy were mainly attributable to first appropriate ATP therapy (31 vs. 18%; $p = 0.007$). Overall appropriate ATP and shocks, as well as appropriate shocks per patient, were significantly higher among digitalis patients (Table 4).

Furthermore, digitalis patients had higher rates of overall first rehospitalization (38 vs. 21%), mainly attributable to VT recurrences and acute HF, as well as a higher rate of all-cause mortality at 5 years (33 vs. 20%) (Table 4).

Stratification by AF and HF

Among the AF patients ($n = 172$), digitalis therapy was associated with decreased freedom from recurrence of ventricular tachyarrhythmia (63 vs. 43%; log-rank $p = 0.060$; HR = 1.505; 95% CI 0.980–2.311; $p = 0.062$, statistical trend) (Fig. 3a, left panel), as well as with decreased freedom from appropriate ICD therapy (53 vs. 34%; log-

rank $p = 0.052$; HR = 1.594; 95% CI 0.992–2.561; $p = 0.054$, statistical trend) (Fig. 3a, right panel). In the presence of “AF only” (without HF), digitalis was still associated with decreased freedom from recurrence of ventricular tachyarrhythmia (69 vs. 38%; log-rank $p = 0.033$; HR = 2.434; 95% CI 1.048–5.650; $p = 0.038$) and ICD therapy (61 vs. 32%; log-rank $p = 0.043$; HR = 2.452; 95% CI 0.099–6.017; $p = 0.050$).

Among the HF patients ($n = 343$), digitalis was not associated with decreased freedom from recurrence (log-rank $p = 0.102$) (Fig. 3b, left panel), but with decreased freedom from appropriate device therapy (52 vs. 34%; log-rank $p = 0.019$; HR = 1.527; 95% CI 1.070–2.178; $p = 0.020$) (Fig. 3b, right panel).

Since the HF group still comprised more patients with concomitant AF, the impact of digitalis was reevaluated after having excluded the AF patients from the HF subgroup. In “HF-only” patients (without AF) ($n = 222$), digitalis was associated with comparable rates of recurrent

Fig. 4. Digitalis therapy was still associated with an increased risk of recurrent VT/VF within the entire study cohort (left columns) and appropriate ICD therapy (right columns) after multivariable adjustment in Cox regression models. Bold denotes significance. AF, atrial fibrillation; HF, heart failure; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; CKD, chronic kidney disease.

ventricular tachyarrhythmia (53 vs. 43%; log-rank $p = 0.362$), whereas higher rates of appropriate ICD therapy were still observed (53 vs. 34%; log-rank $p = 0.053$; HR = 1.590; 95% CI 0.990–2.553; $p = 0.055$, statistical trend) (data not shown).

Multivariable Cox Regression Models

Even after multivariable adjustment, digitalis treatment was still associated with a 1.4-fold higher risk of first recurrence of ventricular tachyarrhythmia (HR = 1.367; 95% CI 0.995–1.880; $p = 0.054$) (Fig. 4, left panel), which was still proven especially for ICD recipients for secondary prevention (HR = 1.588; 95% CI = 1.053–2.394; $p = 0.027$) (data not shown). Accordingly, digitalis treatment was still associated with a 1.6-fold higher risk of appropriate device therapy (HR = 1.598; 95% CI 1.135–2.250; $p = 0.007$) (Fig. 4, right panel).

Discussion

The present study evaluated the prognostic impact of digitalis treatment on the primary endpoint of recurrence of ventricular tachyarrhythmia, as well as on secondary endpoints, such as appropriate ICD therapy, rehospitalization, and all-cause mortality at 5 years of follow-up, in ICD recipients with HF and AF surviving index episodes of ventricular tachyarrhythmia with additional beta-blocker treatment.

This study suggests that digitalis treatment (digoxin in 68% and digitoxin in 32% of the cases) decreases freedom from first recurrent ventricular tachyarrhythmia and from first appropriate device-related therapy. Digitalis especially increased the rates of recurrent sustained VT and of appropriate ATP therapy. Furthermore, negative impacts of digitalis, especially increased rates of appropriate ICD therapy, were seen in patients with HF only and in those with AF only. The adverse prognostic impact of digitalis was also seen after multivariable adjustment. Furthermore, patients treated with digitalis had a higher rate of rehospitalization and all-cause mortality at 5 years.

Focusing on current trends in pharmacotherapeutics, a decline in prescriptions of digoxin was demonstrated within an observational registry including more than 250,000 patients with HF with a reduced ejection fraction (HFrEF) and those with a preserved ejection fraction from 2005 until 2014 [17]. The recommendation to treat patients with digitalis is based on recommendation class II with a level of evidence B, as recently stated within European guidelines, for patients with symptomatic HFrEF to reduce the number of HF-related rehospitalizations [11]. In contrast, digitalis is recommended for patients with AF to control tachycardiac episodes irrespective of the presence of systolic HF (class I recommendation, level of evidence B) [12].

These heterogeneous recommendations for the use of digitalis, especially in HF, are based on recent studies, which demonstrated increasing rates of mortality [15, 24–30].

Although the prognostic impact of digitalis on all-cause mortality has been analyzed in many studies with different findings, there are only few studies that focus on the development of recurrence of ventricular tachyarrhythmia, especially disregarding ICD recipients after they had already survived index episodes of ventricular tachyarrhythmia. Therefore, the present study adds to the scientific evidence about the use of digitalis, since it was demonstrated that digitalis treatment of ICD recipients with HF or AF was especially associated with decreased freedom from appropriate ICD therapy, which was demonstrated in AF and HF patients (even after excluding AF patients). These data therefore support the evidence for a careful use of digitalis in patients surviving ventricular tachyarrhythmias despite the presence of an activated ICD.

Digoxin was evaluated in 350 consecutive HF patients with LVEFs <35% and an activated CRT-D for primary prevention, where it was associated with an increased risk of appropriate shock therapy [19]. Accordingly, the MADIT-CRT trial demonstrated an increased risk of fast VT and VF [18]. Furthermore, Mina et al. [20] retrospectively analyzed 202 patients with either AF, HF (LVEF <45%), or both and observed increased rates of ICD shock, electrical storm, and rehospitalization among 55 patients treated with digoxin at the 1-year follow-up. In contrast to prior ICD studies, the present one applies a different point of view, meaning a “secondary preventive effect” in a higher-risk population, in patients surviving at least one episode of VT. In these patients, treatment with digitalis increased the risk of recurrent episodes of ventricular tachyarrhythmia, appropriate device therapy, rehospitalization, and mortality.

However, besides treatment with digitalis, ventricular arrhythmogenicity is influenced by various factors. Especially AF represents an important predictor of ventricular tachyarrhythmia and SCD. An increased risk of tachyarrhythmia goes along with a higher incidence of short-long cycles that can degenerate into VT among AF patients [9, 31, 32]. It may therefore be assumed that the increased risk of recurrence of ventricular tachyarrhythmia is triggered by the interaction of digitalis and AF, rather than by digitalis therapy its own. Data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) suggest that 62% of AF patients are symptomatic (European Heart Rhythm Association [EHRA] class ≥ 2) and 17% even have severe symptoms (EHRA class 3–4), combined with a decreased quality of life [33]. However, the authors observed a comparable distribution of digoxin use between patients in EHRA class 1 and those in EHRA class >1. In contrast, a

greater supply with digitalis was observed in symptomatic patients than in asymptomatic patients among 2,452 originally symptomatic AF patients at after 1 year of follow-up [34]. The authors of that study found increased risks of cardiac rehospitalization, stroke, and HF, worsening among patients with symptomatic AF. However, this study was not able to separate the interaction of AF symptoms with digitalis use, even when focusing on the subgroup of AF patients only, because there might have been patients with more severe AF symptoms in the digitalis group, which cannot be controlled for retrospectively.

To retrospectively control for some potential confounding due to different pharmacological interactions, all study patients were treated with beta-blockers, which guarantees further homogeneity beyond equally distributed comorbidities and comparability between the two therapeutic regimens. In particular, the European guidelines demand studies evaluating the combined treatment with beta-blockers and digitalis, especially for patients with HFrEF and AF [11]. The combination of beta-blockers and digoxin was analyzed by Lam et al. [35] using a propensity score-matched cohort of 334 patients, observing significantly lower rates of any hospital readmissions at 30 days; no differences in mortality rates were found in the digoxin group. In contrast, the present study found increased rates of rehospitalization especially due to ventricular tachyarrhythmia and acute HF despite beta-blocker treatment after long-term follow-up of 5 years.

In conclusion, this study demonstrates for the first time that treatment with digitalis is associated with an increased risk of – as well as a decrease in freedom from – recurrent ventricular tachyarrhythmias among ICD recipients with HF and/or AF and additional beta-blocker therapy. An increased risk of appropriate ICD therapy was especially evident with secondary preventive ICDs. Digitalis treatment was moreover associated with decreased freedom from appropriate ICD therapy among AF patients and HF patients, even after excluding AF patients.

However, besides digitalis therapy itself, the interaction of digitalis and AF may be an important trigger of recurrences of ventricular tachyarrhythmia. Further studies or even randomized controlled trials are necessary to separate the ways of interaction of digitalis therapy and AF or HF with low LVEF.

Study Limitations

This observational and retrospective registry-based analysis reflects a realistic consecutive picture of the healthcare supply of high-risk patients presenting with

ventricular tachyarrhythmias. The lost-to-follow-up rate regarding the evaluated endpoint of all-cause mortality was minimal. To minimize the lost-to-follow-up rate, all patients not presenting to the ICD follow-up at least one time after discharge were excluded from the analysis. The pharmacological therapies were based on the discharge medication at the index event. Despite multivariable adjustment, a certain prognostic impact of comorbidities in the digitalis group may not be excluded. All clinical data were documented reliably during routine clinical care by individual cardiologists being blinded to the final analyses, obviating the use of an independent clinical event committee. A selection bias due to the inhomogeneous distribution of AF rates may not be excluded, since the risk of recurrent ventricular tachyarrhythmias might be triggered by the interaction of digitalis and AF besides digitalis therapy itself. Moreover, the choice of treating patients with digitalis is made by physicians during routine clinical care. Unmeasured confounding (including the degree of AF or HF symptoms, i.e., NYHA or EHRA

class, as well as important biomarkers, i.e., BNP) may also have affected our results, which may predominantly have occurred in digitalis patients. The present results need to be reevaluated within even more extensive and more representative multicenter registry data or even randomized controlled trials, especially focusing on the effect of digitalis on AF patients, controlling for confounding AF symptoms.

Statement of Ethics

This study was carried out according to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee II of the Medical Faculty Mannheim, Heidelberg University, Germany.

Disclosure Statement

The authors declare that they do not have any conflict of interest.

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