Digitalis therapy in patients with ventricular tachyarrhythmias

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ABSTRACT

Objective. The study sought to assess the prognostic value of treatment with digitalis on long-term prognosis in patients with ventricular tachyarrhythmias and atrial fibrillation (AF) and/or heart failure (HF). Background. Data regarding the outcome of digitalis therapy following ventricular tachyarrhythmias is limited. Methods. A large retrospective registry was used including consecutive patients with episodes of ventricular tachycardia (VT) or fibrillation (VF) from 2002 to 2015. Patients treated with digitalis were compared to patients without. The primary prognostic endpoint was all-cause mortality at 3 years, secondary endpoints comprised a composite arrhythmic endpoint (i.e. recurrences of ventricular tachyarrhythmias, appropriate implantable cardioverter defibrillator (ICD) therapies, sudden cardiac death) and cardiac rehospitalization. Kaplan Mayer survival curves, multivariable cox regression, and time trend analyses were applied for statistics. Results. Eight hundred and thirty-one patients were included (20% treated with digitalis and 80% without). At 3 years, digitalis treatment was not associated with all-cause mortality following ventricular tachyarrhythmias (24 vs. 21%, log-rank \(p = .736\); HR = 1.063; 95% CI 0.746–1.515; \(p = .736\)). However, digitalis therapy was associated with an increased risk of the composite arrhythmic endpoint (38 vs. 23%; log-rank \(p = .001\); HR = 1.719; 95% CI 1.279–2.311; \(p = .001\)) and cardiac rehospitalization (31 vs. 18%; log-rank \(p = .001\); HR = 1.829; 95% CI 1.318–2.538; \(p = .001\)), which was still evident within multivariable Cox regression analyses. Finally, digitoxin may be associated with a worse prognosis than digoxin. Conclusion. Digitalis therapy was not associated with mortality in patients with ventricular tachyarrhythmias, but with increased risk of the composite arrhythmic endpoint and cardiac rehospitalization at 3 years.

Introduction

For symptomatic treatment of systolic heart failure (HF), digitalis glycosides have been used for over 230 years to improve patients’ symptoms, whereas heterogeneous results were published regarding the prognostic impact of digitalis on mortality [1–3]. However, until now, only one randomized controlled trial (RCT), the “DIG trial”, investigated the prognostic role of digoxin in patients with HF and sinus rhythm. The DIG trial failed to demonstrate a significant reduction in mortality but showed a decreased risk of hospitalization as compared to patients treated with a placebo [4]. Due to the lack of further RCT—especially in patients suffering from atrial fibrillation (AF)—digitalis treatment only has a class IIb recommendation within current European guidelines for acute and chronic HF and a class IIa indication for rate control in AF, respectively [5–7]. This led to decreased prescription rates over the past decades [8,9]. In contrast, many observational studies suggested adverse outcomes in patients treated with digitalis as compared to those without [2,3,10]. For instance, a meta-analysis including 19 studies and over 300,000 patients reported a 29% increased risk of mortality in patients treated with digoxin in the presence of AF, and 14% in HF, respectively [2]. This may be related to the narrow therapeutic window of digitalis as well as multiple drug interactions and an increased risk of adverse arrhythmic events. However, data focusing on the risk of arrhythmic endpoints in patients treated with digitalis, predominantly focus on patients undergoing implantable cardioverter defibrillator (ICD) implantation for primary prevention of sudden cardiac death [11,12].

To the best of our knowledge, there is no data available on whether digitalis affects long-term outcomes in patients with ventricular tachyarrhythmias. Therefore, this study evaluates the prognostic impact of digitalis therapy on the primary endpoint of all-cause mortality, as well as on secondary endpoints (i.e. composite arrhythmic endpoint, drug interactions and an increased risk of adverse arrhythmic events).
cardiac rehospitalization) in consecutive patients with ventricular tachyarrhythmias with HF and/or AF despite beta-blocker therapy. Furthermore, the prognosis of patients treated with digoxin is compared to those treated with digi-

toxin. Finally, time trend analyses were performed regarding the prescription rates of digitalis during the study period from 2002 until 2015.

Methods

Data collection and documentation

This is a retrospective study cohort including all patients surviving index episodes of ventricular tachyarrhythmias [i.e. ventricular tachycardia (VT) and ventricular fibrillation (VF)] on admission from 2002 until 2016 at one institution as recently published [13]. The study is derived from an analysis of the “Registry of Malignant Arrhythmia and Sudden Cardiac Death–Influence of Diagnostics and Interventions (RACE-IT)”, a single-center registry including consecutive patients presenting with ventricular tachyar-

rhythmias and aborted cardiac arrest being acutely admitted to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 until 2015. The 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, University of Heidelberg, Germany.

Ventricular tachyarrhythmias comprised ventricular tachycardia (VT) and fibrillation (VF), as defined by current international guidelines [7]. Sustained VT was defined by a duration of >30 s or causing hemodynamic collapse within 30 s. Non-sustained VT was defined by a duration of <30 s both characterized by wide QRS complexes (≥120 ms) at a rate of >100 beats per minute [7]. Ventricular tachyarrhyth-

mias were documented by 12-lead electrocardiogram (ECG), ECG tele-monitoring, ICD, or in case of unstable course or during cardiopulmonary resuscitation (CPR), by external defibrillator monitoring. Documented VF was treated by external defibrillation and in case of prolonged instability with additional intravenous anti-arrhythmic drugs during CPR.

Further data being documented contained baseline char-

acteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies, such as coronary angiography, electrophysiological examination, data being derived from prior or newly implanted cardiac devices, including already implanted at index and implanted cardiac defibrillators (ICD) at follow-up, pacemaker or cardiac con-

tractility modulation (CCM), as well as imaging modalities, such as echocardiography or cardiac magnetic resonance imaging. CKD was defined as abnormalities of kidney func-

tion with health implications accompanied by a glomerular filtration rate (GFR) <60 ml/min/1.73 m² (GFR categories G3a–G5) and a duration >3 months [14].

Inclusion and exclusion criteria

Consecutive patients with HF and/or AF with concomitant beta-blocker therapy were included. All patients had a docu-

mented episode of ventricular tachyarrhythmias, which defines the index event. HF was defined as documented left ventricular ejection fraction (LVEF) <45% [5]. Paroxysmal AF was defined as self-terminating in most cases within 48 h and lately for up to 7 days, including AF episodes that are cardioverted within 7 days. Persistent AF lasts longer than 7 days including episodes terminated by cardioversion either with drugs or by direct current cardioversion after 7 days or more. Permanent AF was defined as accepted by the patient and physician without pursuing further rhythm control. AF patients may include all degrees of LVEF [6].

The decision to treat patients with beta-blocker and digi-

talis was based on the discretion of the cardiologists during routine care according to European guidelines [5,6,15,16]. Patients without HF or AF, those without concomitant beta-blocker treatment, and patients with death during index hospitalization were excluded from the present study.

Definition of case and control groups

The case group (digitalis group) comprised all patients with digitalis and beta-blocker treatment at discharge. Both digoxin and digitoxin, and all types of concomitant beta-blockers were included. The control group (non-digitalis group) comprised all patients with beta-blocker, but without digitalis treatment at index hospital discharge. All other medical therapies apart from beta-blocker and digitalis were allowed.

Primary and secondary endpoints

Follow up period was set at 3 years for all outcomes. The primary prognostic endpoint was all-cause mortality. All-

cause mortality was documented using our electronic hos-

pital information system and by directly contacting state resident registration offices (“bureau of mortality statistics”) all across Germany. Identification of patients was verified by place of name, surname, day of birth, and registered living addresses. Secondary endpoints were a composite endpoint (i.e. recurrences of ventricular tachyarrhythmias, appropriate ICD therapies and sudden cardiac death) and cardiac rehos-

pitalization. Cardiac rehospitalization comprised of rehos-

pitalization due to VT, VF, AMI, acute HF, and inappropriate device therapy.

Statistical methods

Quantitative data are presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data and were compared using the Student’s t-test for normally distributed data or the Mann–Whitney U test for nonparametric data. Deviations from a Gaussian 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 Chi² test or the Fisher’s exact test, as appropriate.

Firstly, the univariable Kaplan–Meier method was applied to evaluate prognostic differences within the entire cohort. Then, the impact of digitalis was analyzed separated for AF and HF, allowing the combination of AF and HF. Secondly, multivariable Cox regression models were developed using the “forward selection” option, where only statistically significant variables \((p < .05)\) 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), acute myocardial infarction (AMI), AF, LVEF <35%, the presence of an ICD and digitalis therapy. Thereafter, the prognosis of patients with digitoxin was compared to those treated with digoxin. Finally, time trend analyses were applied within the entire study cohort, as well as separated for patients with AF and HF. Chi² test was applied to compare frequencies of digitalis prescription rates.

The result of a statistical test was considered significant at \(p < .05\), a statistical trend was defined as \(p < .10\). SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS (Version 25, IBM, Armonk, NY, USA) was used for statistics.

**Results**

**Study population**

From a total of 2422 patients with ventricular tachyarrhythmias, 715 were excluded for in-hospital death, 353 without concomitant beta-blocker treatment, and 523 patients without AF or HF (Figure 1; flow chart). The final study cohort comprised 831 patients with HF (79%), and AF (50%), of which 29% revealed both entities. Within the entire study cohort, 20% of all patients were treated with digitalis and as separate treatments for patients with AF and HF. Chi² test was applied to compare frequencies of digitalis prescription rates.
Table 1. Baseline characteristics.

| Characteristic                                      | Non-digital (n = 667; 80%) | Digital (n = 164; 20%) | p-Value |
|-----------------------------------------------------|-----------------------------|------------------------|---------|
| Study drugs; n (%); mg/day (mean±SEM)               |                             |                        |         |
| Digitoxin                                          | –                           | 60 (37)                | –       |
| Digoxin                                            | –                           | 0.08 ± 0.002           | –       |
| Age, median (range)                                | 69 (20–89)                  | 69 (32–90)             | .002    |
| Male gender, n (%)                                 | 519 (78)                    | 129 (79)               | .814    |
| Body mass index (kg/m²), median (IQR)              | 27 (24–32)                  | 31 (29–34)             | .339    |
| Ventricular tachyarrhythmias at index, n (%)       |                             |                        |         |
| Ventricular tachycardia                            | 414 (71)                    | 128 (78)               | .073    |
| Ventricular fibrillation                            | 193 (29)                    | 36 (22)                |         |
| Inclusion criteria, n (%)                          |                             |                        |         |
| Atrial fibrillation                                | 313 (47)                    | 102 (62)               | .001    |
| Heart failure                                      | 526 (79)                    | 132 (80)               | .646    |
| Atrial fibrillation and heart failure              | 172 (26)                    | 70 (43)                | .001    |
| Cardiovascular risk factors, n (%)                 |                             |                        |         |
| Arterial hypertension                              | 435 (65)                    | 113 (69)               | .372    |
| Diabetes mellitus                                  | 183 (27)                    | 56 (34)                | .089    |
| Hyperlipidemia                                     | 239 (36)                    | 73 (45)                | .040    |
| Smoking                                            | 214 (32)                    | 47 (29)                | .397    |
| Cardiac family history                             | 75 (11)                     | 22 (13)                | .438    |
| Comorbidities at index stay, n (%)                 |                             |                        |         |
| Prior myocardial infarction                        | 229 (34)                    | 55 (34)                | .847    |
| Prior coronary artery disease                      | 359 (54)                    | 95 (58)                | .344    |
| Prior heart failure                                | 234 (35)                    | 88 (54)                | .001    |
| Atrial fibrillation                                | 313 (47)                    | 102 (62)               | .001    |
| Paroxysmal                                         | 221 (33)                    | 64 (39)                | .001    |
| Persistent                                         | 27 (4)                      | 15 (9)                 | .404    |
| Chronic kidney disease                             | 65 (10)                     | 23 (14)                |         |
| Non-ischemic cardiomyopathy                        | 72 (11)                     | 29 (18)                | .016    |
| Cardiopulmonary resuscitation                      | 179 (27)                    | 29 (17)                | .011    |
| Coronary angiography, n (%)                        | 2146 (603–7007)             | 2146 (666–6287)        | .826    |
| Coronary angiography                                | 455 (68)                    | 93 (57)                | .005    |
| No evidence of CAD                                  | 104 (23)                    | 21 (23)                | .800    |
| 1-vessel disease                                   | 107 (24)                    | 19 (20)                |         |
| 2-vessel disease                                   | 105 (23)                    | 20 (22)                |         |
| 3-vessel disease                                   | 139 (31)                    | 33 (36)                |         |
| Chronic total occlusion                            | 103 (23)                    | 26 (28)                | .271    |
| Presence of CABG                                   | 81 (18)                     | 26 (28)                | .024    |
| PCI                                                | 175 (39)                    | 24 (26)                | .021    |
| Acute myocardial infarction                        | 166 (23)                    | 18 (11)                | .001    |
| STEMI                                              | 64 (10)                     | 3 (2)                  | .001    |
| NSTEMI                                             | 102 (15)                    | 15 (9)                 | .043    |
| Hyperkalemia                                       | 4 (1)                       | 1 (1)                  | 1.000   |
| Hypokalemia                                        | 40 (6)                      | 12 (7)                 | .532    |
| LVEF, n (%)                                        | 63 (10)                     | 14 (9)                 | .003    |
| ≤55%                                               | 38 (6)                      | 5 (3)                  |         |
| 54–45%                                             | 203 (32)                    | 30 (20)                |         |
| 44–35%                                             | 323 (52)                    | 102 (68)               |         |
| Not documented                                     | 40                          | 13                     |         |
| Cardiac therapies at index, n (%)                  |                             |                        |         |
| Electrophysiological examination                   | 199 (30)                    | 61 (37)                | .069    |
| VT ablation therapy                                | 54 (8)                      | 6 (4)                  | .049    |
| Presence of an ICD, n (%)                          | 417 (63)                    | 131 (80)               | .001    |
| Medication at discharge, n (%)                     |                             |                        |         |
| Beta-blocker*                                      | 667 (100)                   | 164 (100)              | 1.000   |
| ACE-inhibitor                                      | 489 (73)                    | 115 (70)               | .411    |
| ARB                                                | 77 (12)                     | 26 (16)                | .135    |
| Statin                                             | 457 (69)                    | 110 (67)               | .722    |
| Amiodarone                                         | 152 (23)                    | 30 (18)                | .213    |
| Aldosterone antagonist                             | 110 (17)                    | 34 (21)                | .199    |

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment myocardial infarction; NT-pro BNP: N-terminal prohormone of brain natriuretic peptide; PCI: percutaneous coronary intervention; SEM: standard error of mean; STEMI: ST-segment MI; VT: ventricular tachycardia.

Bold type indicates p < .05.

*All patients were treated with beta-blockers by inclusion criteria.
the primary endpoint of all-cause mortality occurred in 24% of the patients with digitalis treatment and 21% without. Accordingly, the risk of all-cause mortality was not affected by treatment with digitalis (log-rank \( p = .736 \); HR = 1.063; 95% CI 0.746–1.515; \( p = .736 \)) (Table 2 and Figure 2, left panel). In contrast, digitalis was associated with the composite endpoint (38 vs. 23%; log-rank \( p = .001 \); HR = 1.719; 95% CI 1.279–2.311; \( p = .001 \)) and the risk of cardiac rehospitalization at 3 years (31 vs. 18%; log-rank \( p = .001 \); HR = 1.829; 95% CI 1.318–2.538; \( p = .001 \)) (Figure 2, middle and right panel).

### Stratification by atrial fibrillation and heart failure

Characteristics of patients, stratified by AF and HF, are presented in Table 3. In AF patients (\( n = 415 \)), VT was more common in patients treated with digitalis than in patients without (80 vs. 70%; \( p = .041 \)). In line, LVEF < 35% was more common in AF patients on digitalis treatment (61 vs. 44%; \( p = .025 \)). In patients with AF, digitalis use was not associated with the primary endpoint of all-cause mortality at 3 years (27 vs. 24%; log-rank \( p = .963 \); HR = 1.011; 95% CI 0.651–1.568; \( p = .963 \)) (Figure 3(A), left panel). The composite endpoint (38 vs. 20%; log-rank \( p = .001 \); HR = 1.957; 95% CI 1.312–2.917; \( p = .001 \)) and rehospitalization (31 vs. 18%; log-rank \( p = .005 \); HR = 1.837; 95% CI 1.190–2.837; \( p = .006 \)) were more common in patients treated with digitalis (Figure 3(A), middle and right panel).

### Follow-up data, primary, and secondary endpoints within the entire study cohort

The median follow-up time within the entire study cohort was 4.0 years (IQR 1.7–7.5 years). At 3 years of follow-up, 80% without (\( p = .001 \)). Accordingly, 20% of HF patients and 25% of AF patients were treated with digitalis (paroxysmal AF 23%, persistent AF 36%, and permanent AF 26%). Target dosages were already reached at discharge, as seen for digoxin in 63% (mean dosage 0.14 mg per day) and for digitoxin in 37% (mean dosage 0.08 mg per day) (Table 1).

As seen in Table 1, patients were median-aged at 69 years and most patients were males (78%). An index episode of VT was more common than VF (71–78% vs. 22–29%; \( p = .073 \)). The overall rates of HF (i.e. LVEF < 45%) were comparable between digitalis and non-digitalis (79 vs. 80%; \( p = .646 \)), whereas significantly more digitalis patients suffered from AF (62 vs. 47%; \( p = .001 \)). Cardiovascular risk factors were equally distributed within both groups, except for a higher rate of hyperlipidaemia in patients with digitalis treatment (45 vs. 36%; \( p = .040 \)). Especially the rates and extent of coronary artery disease and the rate of chronic kidney disease were similar in both groups, whereas more patients with digitalis therapy had an LVEF < 35% (68 vs. 52%; \( p = .003 \)). In contrast, concomitant pharmacological treatment regarding angiotensin-converting enzyme inhibitors (ACEI), receptor blockers (ARB), and amiodarone were comparable.

### Table 2. Primary and secondary endpoints, follow-up data.

| Characteristics                  | Non-digitalis (\( n = 667; 80\% \)) | Digitalis (\( n = 164; 20\% \)) | \( p\)-Value |
|----------------------------------|-------------------------------------|---------------------------------|------------|
| **Primary endpoint, n (%)**      |                                     |                                 |            |
| All cause-mortality, at 3 years  | 142 (21)                            | 39 (24)                         | .489       |
| **Secondary endpoints, n (%)**  |                                     |                                 |            |
| Cardiac rehospitalization, at 3 years | 120 (18)                         | 51 (31)                         | .001       |
| Composite endpoint (recurrent ventricular tachyarrhythmias; ICD therapies, sudden cardiac death), at 3 years | 151 (23) | 62 (38) | .001 |
| **Follow-up times, n (%)**      |                                     |                                 |            |
| Hospitalization time; days [median (IQR)] | 13 (8–23)                           | 16 (8–27)                       | .473       |
| ICU time; days [median (IQR)]    | 3 (0–8)                             | 1 (0–7)                         | .029       |
| Survival time; days [mean; median (range)] | 1700; 1385 (12–5106) | 2043; 1743 (20–5089) | .059 |

ICD: implantable cardioverter-defibrillator; ICU: intensive care unit; IQR: interquartile range.

Level of significance \( p \leq .05 \).

Bold type indicates \( p \leq .05 \).

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Figure 2. Prognostic impact of digitalis treatment on all-cause mortality (left panel), risk of the composite endpoint (i.e. recurrence of ventricular tachyarrhythmias, sudden cardiac death) (middle), and cardiac rehospitalization (right) within the entire study.
Similar observations were made for patients suffering from HF (i.e. LVEF <45%) regarding all-cause mortality (23 vs. 21%; log rank p = 0.956; HR = 1.011; 95% CI 0.675–1.515; p = 0.617) the composite endpoint (39 vs. 25%; log rank p = .003; HR = 1.620; 95% CI 1.174–2.234; p = .003) and cardiac rehospitalization (36 vs. 20%; log rank p = .001; HR = 1.945; 95% CI 1.382–2.737; p = .001) (Figure 3(B)).

Subsequently, patients with the combination of AF and HF (n = 242) were analysed. In patients with AF and HF, all-cause mortality at 3 years was comparable among patients with and without digitalis treatment (26 vs. 26%; log-rank p = .617; HR = 0.869; 95% CI 0.502–1.505; p = .617). In contrast, digitalis therapy increased the risk of the composite endpoint (41 vs. 24%; log-rank p = .028; HR = 1.688; 95% CI 1.052–2.710; p = .030) and cardiac rehospitalization (41 vs. 24%; log-rank
After multivariable adjustment, digitalis was not associated with the risk of all-cause mortality at 3 years (HR = 0.982; 95% CI 0.663–1.453; p = .927) (Table 4). In contrast, increasing age (HR = 1.039; p < .001), presence of diabetes mellitus (HR = 1.763; p < .001), chronic kidney disease (HR = 1.583; p = .004), and LVEF < 35% (HR = 1.651; p = .004) were associated with an impaired prognosis, whereas an ICD was associated with decreased long-term mortality (HR = 0.438; p = .001). Finally, the risk of the composite endpoint (HR = 1.412; 95% CI 1.025–1.946; p = .035) and the risk of cardiac rehospitalization (HR = 1.561; 95% CI 1.101–2.215; p = .012) were increased in patients treated with digitalis as compared to those without (Table 4).

**Multivariable cox regression models**

Within the entire study cohort, 63% of patients with digitalis were treated with digoxin and 37% with digitoxin.
At 3 years of follow-up, treatment with digitoxin was associated with worse long-term survival as compared to digoxin (38 vs. 15%; log-rank $p = .001$; HR = 3.033; 95% CI 1.600–5.752; $p = .001$) (Figure 4). The adverse prognosis was still evident after multivariable Cox regression analysis (HR = 1.988; 95% CI 0.952–4.154; $p = .068$; statistical trend) (not shown). In contrast, secondary endpoints were not affected by the type of digitalis treatment (i.e. digoxin vs. digitoxin).

**Table 4. Multivariable cox regression analyses.**

| Endpoint            | HR     | 95% CI         | p-Value |
|---------------------|--------|----------------|---------|
| **Mortality**       |        |                |         |
| Age                 | 1.039  | 1.021–1.057    | .001    |
| Gender              | 1.428  | 0.965–2.114    | .075    |
| Diabetes            | 1.763  | 1.288–2.412    | .001    |
| Chronic kidney disease | 1.583 | 1.155–2.170    | .004    |
| AMI                 | 0.669  | 0.441–1.015    | .059    |
| AF                  | 1.211  | 0.881–1.664    | .237    |
| LVEF <35%           | 1.651  | 1.171–2.326    | .004    |
| Presence of ICD     | 0.438  | 0.310–0.619    | .001    |
| Digitalis           | 0.982  | 0.663–1.453    | .927    |
| **Composite endpoint** |      |                |         |
| Age                 | 1.004  | 0.991–1.017    | .530    |
| Gender              | 0.954  | 0.670–1.359    | .795    |
| Diabetes            | 0.691  | 0.497–0.961    | .028    |
| Chronic kidney disease | 1.013 | 0.762–1.346    | .930    |
| AMI                 | 0.941  | 0.626–1.415    | .770    |
| AF                  | 1.021  | 0.765–1.363    | .889    |
| LVEF <35%           | 1.051  | 0.777–1.423    | .746    |
| Presence of ICD     | 5.828  | 3.419–9.933    | .001    |
| Digitalis           | 1.412  | 1.025–1.946    | .035    |
| **Rehospitalization** |      |                |         |
| Age                 | 1.009  | 0.994–1.024    | .234    |
| Gender              | 0.959  | 0.648–1.419    | .833    |
| Diabetes            | 1.029  | 0.732–1.446    | .871    |
| Chronic kidney disease | 1.117 | 0.813–1.534    | .495    |
| AMI                 | 1.513  | 1.023–2.236    | .038    |
| AF                  | 1.167  | 0.846–1.610    | .345    |
| LVEF <35%           | 1.191  | 0.847–1.675    | .314    |
| Presence of ICD     | 3.491  | 2.157–5.650    | .001    |
| Digitalis           | 1.561  | 1.101–2.215    | .012    |

AMI: acute myocardial infarction; CI: confidence interval; CPR: cardiopulmonary resuscitation; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; AF: atrial fibrillation. Bold type indicates statistical significance. Level of significance $p \leq .05$.

**Time trend analyses**

Finally, we investigated whether digitalis treatment has changed during the study period (2002 until 2015). In patients with AF and/or HF, digitalis treatment decreased from 46.9% in 2002 to 7.5% in 2015 ($p = .001$ for the trend). This trend was observed in both patients with AF (i.e. 53.8% to 7.7%; $p = .001$) and HF (i.e. 46.4% to 6.7%; $p = .001$) (Figure 5).

**Discussion**

The present study evaluates the prognostic impact of digitalis treatment on the primary endpoint of all-cause mortality, as well as on secondary endpoints, such as a composite arrhythmic endpoint (i.e. recurrence of ventricular tachyarrhythmias, appropriate ICD therapies, sudden cardiac death).
and cardiac rehospitalization at 3 years in patients surviving index episodes of ventricular tachyarrhythmias.

During the study period from 2002 until 2015, treatment with digitalis decreased from 46.9 to 7.5%. This trend was observed both in patients suffering from AF and HF. The present study suggests that digitalis treatment (digoxin in 67% and digitoxin in 37%) is not associated with increased mortality in patients with ventricular tachyarrhythmias. However, digitalis treatment may increase the risk of the composite endpoint and the risk of cardiac rehospitalization, which was consistent after multivariable Cox regression analyses and which was seen both in patients with AF and HF, as well as in those patients suffering from both AF and HF. Finally, digitoxin may be associated with increased mortality as compared to digoxin.

Although many observational studies are focusing on the risk of all-cause mortality in patients with AF and/or HF depending on digitalis treatment, it remains unclear whether digitalis treatment independently increases the risk of adverse outcomes, or whether digitalis is more likely prescribed for patients with more advanced stages of cardiovascular disease, who have per se impaired long-term prognosis [17,18]. Besides studies focusing on AF and/or HF, limited data is available focusing on patients with high risk for ventricular tachyarrhythmias, despite the knowledge that digitalis treatment increases the chance of arrhythmias due to oscillatory afterpotentials and cardiac automaticity [19]. Erath et al. included 1020 patients with an ICD for primary or secondary prevention of sudden cardiac death, to evaluate the prognostic value of digitalis treatment (digoxin or digitoxin) on long-term outcomes at ten years. They demonstrated an increased risk of arrhythmic death and cardiac non-arrhythmic death in patients treated with digitalis. However, only 42% of the patients underwent ICD implantation for secondary prevention and arrhythmic events besides arrhythmic death were beyond the scope of this study [10]. In contrast, the present study investigates the risk of long-term outcomes depending on digitalis treatment for “secondary prevention” of sudden cardiac death. Although no mortality differences were observed, the study confirms the findings by Erath et al., demonstrating an increased risk of the composite arrhythmic endpoint, which was still significant after multivariable adjustment, and which was demonstrated within all analysed subgroups. In line, the risk of arrhythmic events in patients treated with digitalis was investigated within a cohort of 169 HF patients undergoing cardiac resynchronization (CRT) implantation. During a median follow-up of almost two years, digitalis therapy was associated with an increased risk of appropriate ICD therapy. Besides digitalis treatment, low LVEF and history of non-sustained VT decreased the freedom from appropriate ICD therapy [11]. Similar observations, suggesting impaired prognosis in patients treated with digitalis were made by Stein et al., including 1703 ICD at one year of follow-up [12]. While most studies focused on the prognostic value of digoxin rather than digitoxin, comparisons of both digitalis glycosides are still rare. However, comparable outcomes of patients treated with digoxin and digitoxin were observed within the ICD cohort of Erath et al. [10] Our study, however, found an increased risk of all-cause mortality in patients treated with digitoxin as compared to digoxin, which should be interpreted with caution due to the small number of patients in the digitoxin-group.

Besides digitalis therapy, the risk of arrhythmic endpoints is affected by multiple pharmacotherapies, especially beta-blockers and amiodarone [20]. Thus, it was recently demonstrated that beta-blockers reduce the risk of ventricular tachycardias leading to syncopes within 226 ICD recipients [21]. To decrease the chance of possible selection bias caused by heterogeneous pharmacological regimes in our study, only patients with concomitant beta-blocker treatment were included. In contrast, rates of beta-blocker therapy range from 68 to 86% within studies focusing on digitalis treatment in ICD cohorts [10,12]. Whether digitalis therapy itself increases the risk of arrhythmic events in patients with ventricular tachyarrhythmias or whether patients on digitalis have an increased risk of arrhythmic events due to increased severity of cardiovascular disease needs to be investigated within further RCT.

Finally, the risk of all-cause mortality in patients treated with digoxin may depend on serum digoxin concentration. A decrease of the serum digoxin concentration by 0.5 ng/ml was shown to be associated with a 19% higher risk of all-cause death among 5824 AF patients with and without concomitant AF. The highest risk of all-cause death was shown in patients with serum digoxin concentration ≥ 1.2 ng/ml [22]. Similar findings were observed in a study by Muk et al., suggesting a serum digoxin concentration ≥ 0.9 ng/ml was associated with the highest risk of death in 580 HF patients [23]. Further studies are necessary to investigate the prognostic role of serum digoxin concentration on arrhythmic endpoints.

In conclusion, this study demonstrates that the treatment with digitalis has significantly decreased in Germany during the past decade (i.e. 46.9–7.5% from 2002 until 2015). However, digitalis was not independently associated with mortality in patients with ventricular tachyarrhythmias with AF and/or HF. In contrast, the risk of the composite arrhythmic endpoint and cardiac rehospitalization was increased in patients with digitalis treatment, which was consistent within multivariable Cox regression analyses and which was observed in the presence of AF and HF. In line, digoxin may be associated with an even worse prognosis as compared to digoxin.

**Study limitations**

The main study limitation is the retrospective, observational and non-randomized study design. Pharmacological therapies were based on discharge medication at the index event. Furthermore, serum digoxin and digitoxin concentrations were beyond the scope of the present study. Despite the multivariable adjustment, a certain prognostic impact of comorbidities in the digitalis group may not be excluded. Unmeasured confounding due to the severity of HF and/or
AF symptoms may also affect our results, which may predominantly be present in digitalis patients. Thus, the severity of symptoms expressed by the New York Heart Association (NYHA) class and European Heart Rhythm Association (EHRA) score was only available in a minor part of the study population and therefore could not be taken into account. The present results need to be re-evaluated within an even larger and more representative multicentre registry data or even randomized controlled trials, especially focusing on the effect of digitalis in AF patients controlling for confounding AF symptoms.

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