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ORIGINAL PAPER

Digitalis therapy is associated with higher comorbidities and poorer prognosis in patients undergoing ablation of atrial arrhythmias: data from the German Ablation Registry

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Abstract

Background Digitalis glycosides are employed for rate control of atrial fibrillation. Recent studies suggested potential harmful effects of digitalis monotherapy and combination with antiarrhythmic drugs. The aim of the present study was to assess the prevalence and potential impact of digitalis therapy on outcome in patients undergoing catheter ablation of supraventricular arrhythmias.

Methods and results The German Ablation Registry is a nationwide, prospective registry with a 1-year follow-up investigating 12,566 patients receiving catheter ablations of supraventricular arrhythmias in 52 German centres. The present analysis focussed on pharmacotherapy in 8608 patients undergoing catheter ablation of atrial tachycardia, atrial fibrillation, or atrial flutter. Patients receiving digitalis therapy ($n=417$) were older and presented a significantly increased prevalence of comorbidities including coronary artery disease, heart failure, diabetes, and pulmonary disease. One-year mortality was significantly higher in digitalis-treated patients (4.7% vs. 1.3%, $p<0.001$), most strikingly in patients undergoing ablation of atrial flutter. This effect was maintained after adjustment for important risk factors. Similar results were obtained for as the combined endpoint of death, myocardial infarction, stroke and major bleeding (6.6% vs. 2.7%, $p<0.001$), and non-fatal rehospitalisations (54.1% vs. 45.1%, $p=0.001$).

Conclusion In the present study of patients undergoing catheter ablation of supraventricular arrhythmias, an association of digitalis therapy with increased mortality and an increased rate of other severe adverse events were observed. The results from this 'real-life' registry are consistent with previously published studies. However, whether digitalis therapy promotes a poorer prognosis or may just serve as a marker for this aspect cannot be thoroughly interpreted.

Keyword Catheter ablation · Supraventricular arrhythmias · Digitalis · Antiarrhythmic drugs

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Introduction

Digitalis glycosides have traditionally been employed for pharmacological treatment of heart failure. Nowadays, its impact for symptomatic treatment of heart failure has been diminished. Current guidelines of the European Society of Cardiology (ESC) indicate that digitalis therapy may be considered in patients with symptomatic heart failure, sinus rhythm and impaired left ventricular function to reduce heart failure hospitalizations [1]. However, digitalis therapy still plays an important role in management of atrial fibrillation (AF). In the current ESC, guidelines for management of AF digitalis are recommended on the same level as other agents such as beta-blocker or verapamil/diltiazem [2]. In particular, digitalis is recommended for rate control in hemodynamically unstable patients, as it does not exert relevant effects on blood pressure.

However, experimental and clinical data have questioned the beneficial effects of digitalis therapy. In the PALLAS trial [3] which was designed to examine the effects of dronedarone in long-standing persistent AF and heart failure, an increased mortality was observed in the dronedarone group leading to premature termination of the study. This effect was at least partially attributed to potential interactions between digitalis therapy and antiarrhythmic drug treatment [4]. Of note, in this study in the dronedarone group, digoxin levels were in median 1.1 ng/ml, which is above the level which has been shown to be associated with an increased mortality in the DIG trial [5], which may also have contributed to the observed effects [4]. Experimental data in isolated hearts supported this assumption, as an increased vulnerability in combination with significantly reduced refractory periods was observed for the combination of dronedarone and digitalis glycosides [6]. These effects were not observed for the combination of amiodarone and digitalis glycosides in the same model [7]. Of note, in both studies, digitalis therapy alone also increased the risk of ventricular arrhythmias. However, these studies were performed with ouabain and not with clinically available digitalis glycosides. This limits the translation of the results to the clinical setting.

In the present study, data from a multi-center real-world registry on patients undergoing catheter ablation of supraventricular arrhythmias were analyzed in the light of potential impact of digitalis therapy. Furthermore, potential effects of concomitant antiarrhythmic drug therapy have also been examined.

Methods

The German Ablation Registry is a nationwide, prospective database of catheter ablations in Germany which is organised by the Stiftung Institut für Herzinfarktforschung Ludwigshafen, Germany (IHF). Fifty-two voluntarily participating German centers committed themselves to include all consecutive consented patients. The registry was approved by the local ethics committees. Details of the study design and procedures and overall results have been published previously [8–12].

The present study includes patients undergoing catheter ablation of atrial fibrillation, atrial flutter, and focal atrial tachycardia. Exclusion criteria of the present analysis were AV-nodal ablation and the presence of electrical heart disease. Two patients who died in hospital and 12 further patients without documented discharge medication could not be included in the present analyses. Follow-up contacts were scheduled prospectively at 1 year after catheter ablation by telephone. The follow-up was performed centrally by the IHF. During telephone contact, standardized questions on arrhythmias (e.g., syncope, resuscitation, and ablation), cardiac events (e.g., myocardial infarction and revascularization), complications, medication, and heart failure symptoms were posed. In case of an ineffective call, further information was gathered from other caring physicians or civil registration offices.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as number and percentage of patients. Differences of categorical distributions were tested for statistical significance using χ^2 tests and odds ratios with 95%-confidence intervals were calculated. Rates of rare complications were compared using Fisher's exact test. The incidence of death and combined endpoints of death, myocardial infarction, and stroke during follow-up was assessed using methods of survival analysis (Kaplan–Meier estimator, log-rank test, and Cox regression). Determinants for the prescription of digitalis were analyzed in a multivariable logistic regression model.

The differences in baseline characteristics between the treatment groups were adjusted for using propensity score methods. The propensity score was estimated as the probability to receive digitalis in a multiple logistic regression model. Model discrimination was assessed by the C statistic, model fit using the Hosmer–Lemeshow test. Clinically relevant variables associated with both treatment and outcome were included: age, sex, type of arrhythmia, (long-standing) persistent atrial fibrillation, implanted device, implanted CRT, NYHA class II or worse, categories of LVEF, diabetes, COPD, structural heart disease, coronary artery disease, procedural success, prior ablation, and the discharge medications ARB/ACE inhibitors, beta-blockers, diuretics, statins, and antiarrhythmic medication classes I, III, and IV. Interactions with type of arrhythmia were checked observing the model fit. For the subjects in the control group, sampling

weights were calculated as the odds of the propensity score. This weighting leads to a selection of control patients similar to the digitalis group, and yields the average treatment effect on the treated (ATT). The achieved covariate balance was assessed by the standardized mean difference, considering absolute values > 0.1 to be indicative of potential relevant confounding [13]. For the comparison of 1-year mortality, the weighted Kaplan–Meier estimator and weighted log-rank test were used [14].

P values ≤ 0.05 were considered statistically significant. The statistics shown should be regarded as descriptive and were based on the available cases. All calculations were performed using the SAS 9.4 software package (SAS Institute, Cary, NC, USA). For the validation of the propensity score calculations, the "twang" package in R version 3.2.3 was used.

Results

Patient characteristics/demographics

Demographic characteristics are summarized in Table 1. Out of 12,566 patients registered in the German Ablation Registry, 8608 patients met the inclusion and exclusion criteria. Comparisons were made between patients with digitalis therapy at discharge ($n = 417$) and patients without digitalis therapy ($n = 8191$). Patients undergoing digitalis therapy were significantly older with a mean age of 66.1 ± 10.1 years than patients without digitalis (62.7 ± 11.3, $p < 0.001$). Consequently, the proportion of patients with 75 years of age or older was significantly elevated in the digitalis group (16.5% vs. 9.7%, $p < 0.001$). Cardiovascular disease was present more often in digitalis-treated patients (65.7%) as compared with controls (43.9%, $p < 0.001$). This was consistent for the presence of coronary artery disease (33.6% vs. 23.3%, $p < 0.001$), history of myocardial infarction (9.1% vs 6.2%, $p = 0.019$) and hypertensive heart disease (20.1% vs. 13.6%, $p < 0.001$). A significantly impaired left ventricular function was observed more often in digitalis-treated patients (LVEF ≤ 40%: 21.0% vs. 7.6%, $p < 0.01$; LVEF ≤ 30%: 10.4% vs. 2.5%, $p < 0.001$). NYHA class II or worse was also more often registered in digitalis-treated patients (60.6% vs. 47.2%, $p < 0.001$). Relevant comorbidities were observed more frequently in the digitalis group. Furthermore, cardiac device therapy was established more often in the digitalis group (18.0% vs. 7.9%, $p < 0.001$, Table 1). Regarding ablation of AF, persistent or long-standing persistent AF (54.1% vs. 36.2%, $p < 0.001$) were observed more frequently in digitalis-treated patients. Paroxysmal AF was reported more frequently in patients without digitalis therapy (51.5% vs. 43.3%, $p < 0.001$).

Determinants of digitalis prescription are shown in Table 2. Of note, in particular, the presence of long-standing persistent AF, structural heart disease, heart failure, diabetes, an implanted device, or failure of ablation procedure was associated with digitalis prescription after catheter ablation.

Table 1 Baseline patient characteristics

	Digitalis therapy	Control group	Odds ratio (95%-confidence interval)	*p* value	Standardized mean difference
Number of patients	($n = 417$)	($n = 8191$)			
Age (years)	66.1 ± 10.1	62.7 ± 11.3		< 0.001	+ 0.32
Male (%)	64.7	69.9	0.79 (0.64–0.97)	0.024	− 0.11
LVEF > 50% (%)	58.8	80.1	0.35 (0.29–0.44)	< 0.001	− 0.48
LVEF < 30% (%)	10.4	2.5	4.55 (3.16–6.53)	< 0.001	+ 0.33
Coronary artery disease (%)	33.6	23.3	1.66 (1.35–2.05)	< 0.001	+ 0.23
Hypertension (%)[a]	66.7	62.1	1.22 (0.74–2.02)	0.43	+ 0.10
Diabetes (%)	25.7	10.8	2.86 (2.27–3.61)	< 0.001	+ 0.39
COPD (%)[a]	9.7	3.2	3.23 (1.40–7.49)	0,004	+ 0.27
NYHA class (%) II or worse[b]	60.6	47.2	1.72 (1.32–2.21)	< 0.001	+ 0.27
Pacemaker (%)	10.6	6.1	1.81 (1.31–2.50)	< 0.001	+ 0.16
ICD (%)	5.8	1.7	3.59 (2.30–5.60)	< 0.001	+ 0.22
CRT (%)	2.6	0.2	13.84 (6.38–30.02)	< 0.001	+ 0.21

LVEF left ventricular ejection fraction, *COPD* chronic obstructive pulmonary disease, *ICD* implantable cardioverter/defibrillator, *CRT* cardiac resynchronization therapy

[a]Data available in a subset of patients only

[b]In patients with structural heart disease

Ablation procedure and discharge

In total, 4.439 patients (51.6%) underwent catheter ablation of atrial fibrillation and 3.743 patients (43.5%) underwent catheter ablation of atrial flutter of atrial macro-reentrant tachycardia. The remaining 426 patients (4.9%) underwent ablation of focal atrial tachycardia. Of note, the proportion of patients undergoing ablation of atrial flutter or atrial macro-reentrant tachycardia was significantly higher in patients receiving digitalis (53.2% vs. 43.4%, $p < 0.001$) which may be due to the fact that rate control in atrial flutter is often less effective. The number of patients undergoing ablation of atrial fibrillation was lower in digitalis-treated patients (43.4% vs. 52.0%, $p < 0.001$). Radiofrequency ablation was more often applied in digitalis-treated patients (93.3% vs. 89.1%, $p = 0.006$), while cryo ablation was more frequently employed in patients without digitalis therapy (6.5% vs. 10.3%, $p = 0.010$). Of note, procedural success (determined by the individual operator) was more often reported in patients without digitalis therapy than in digitalis-treated patients (95.9% vs. 90.4%, $p < 0.001$). Procedural failure was more frequently reported in digitalis-treated patients (5.0% vs. 1.8%, $p < 0.001$).

Table 2 Determinants for prescription of digitalis glycosides at discharge

Variable	Odds Ratio (95%-CI)	*p* value
Age ≥ 70 years	1.23 (0.99–1.53)	0.054
Female gender	1.44 (1.16–1.78)	0.010
Long-standing persistent AF	1.61 (1.26–2.05)	< 0.001
HFrEF (LVEF ≤ 40% and NYHA II+)	2.10 (1.53–2.87)	< 0.001
Structural heart disease	1.86 (1.48–2.33)	< 0.001
Diabetes	2.32 (1.82–2.96)	< 0.001
Implanted device	1.98 (1.49–2.61)	< 0.001
Failure of ablation procedure	2.24 (1.57–3.21)	< 0.001

HFrEF heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction, *AF* atrial fibrillation

Regarding procedural complications in hospital no significant differences were observed between both groups regarding non-fatal myocardial infarction, stroke, or major bleeding. The duration of hospitalization also did not differ between both groups. Regarding most of potential minor complications, no significant differences were observed. In the digitalis group, relevant pericardial effusions (1.5% vs. 0.6%, $p = 0.033$) were reported more often in digitalis-treated patients reflecting the more significant comorbidities and higher patient age in this group.

Regarding medication at discharge beta-blockers was prescribed more often in digitalis-treated patients (85.6% vs. 73.0%, $p < 0.001$). In contrast, antiarrhythmic drugs were administered more often in patients not treated with digitalis (42.1% vs. 29.0%, $p < 0.001$). This difference was mainly based on prescription of class-I antiarrhythmic drugs (23.6% vs. 8.4%, $p < 0.001$), while no significant differences were observed for class-III antiarrhythmic drugs. Differences regarding other cardiovascular medication are displayed in Table 3.

Follow-up

Follow-up information was obtained for 97.8% of patients in the digitalis group and 98.0% of patients without digitalis treatment. Mean follow-up duration was 529.5 ± 122.4 days and 528.6 ± 124.6 days, respectively.

The Kaplan–Meier estimate of 1-year mortality was significantly increased in digitalis-treated patients (4.7% vs. 1.3%, $p < 0.001$, Table 4). Similar results were observed for the combined endpoints death and myocardial infarction (4.7% vs. 1.6%, $p < 0.001$), death, myocardial infarction, and stroke (5.4% vs. 2.2%, $p < 0.001$) as well as death, myocardial infarction, stroke, and major bleeding (6.6% vs. 2.7%) that all occurred more often in digitalis-treated patients. Other non-fatal complications were also registered more frequently in digitalis-treated patients (4.1% vs. 2.1%, $p = 0.014$). Major bleeding alone was also observed more often in the digitalis group (2.0% vs. 0.9%, $p = 0.041$).

Table 3 Cardiovascular medication at time of index discharge

	Digitalis group	Control group	Odds ratio (95%-confidence interval)	*p* value	Standardized mean difference
Number of patients	*n* = 417	*n* = 8191			
ACE-inhibitor/AT1-receptor antagonist	67.9%	48.9%	2.20 (1.79–2.72)	< 0.001	+ 0.39
Betablocker	85.6%	73.0%	2.20 (1.67–2.90)	< 0.001	+ 0.31
Diuretics	55.2%	26.5%	3.41 (2.80–4.16)	< 0.001	+ 0.61
Class-I antiarrhythmic drugs	8.4%	23.6%	0.30 (0.21–0.42)	< 0.001	− 0.42
Class-III antiarrhythmic drugs	16.1%	17.9%	0.88 (0.67–1.15)	0.34	− 0.05
Class-IV antiarrhythmic drugs	5.8%	2.2%	2.76 (1.78–4.29)	< 0.001	+ 0.19
Statin	46.5%	32.0%	1.85 (1.52–2.25)	< 0.001	+ 0.30

Implantation of cardiovascular devices was also observed more often in digitalis-treated patients during follow-up (8.0% vs. 4.2%, $p<0.001$). This accounted for both pacemaker systems (5.8% vs. 3.4%, $p=0.014$) and implantable cardioverter–defibrillator systems (2.2% vs. 0.9%, $p=0.011$). Re-hospitalization was also observed more often in digitalis-treated patients (54.1% vs. 45.1%, $p=0.001$).

Of note, an association with increased mortality was also observed for digitalis-treated patients after adjustment for important risk factors such as age, sex, heart failure (defined as symptomatic heart failure with severely impaired left ventricular function), and diabetes (Fig. 1). This increased mortality was mainly based on significant differences in patients undergoing ablation of atrial flutter. However, a numerically increased mortality was also observed in patients undergoing ablation of AF or focal atrial tachycardia.

To complete the data analysis and exclude a selection bias more thoroughly, a propensity score analysis was performed. Therefore, type of arrhythmia as well as clinically relevant variables associated with both treatment and outcome were included (Tables 5 and 6). Of note, the effects observed in the initial analysis were preserved in this propensity matching model. Most important, a significantly increased mortality was also observed in this analysis in digitalis-treated patients (Fig. 2).

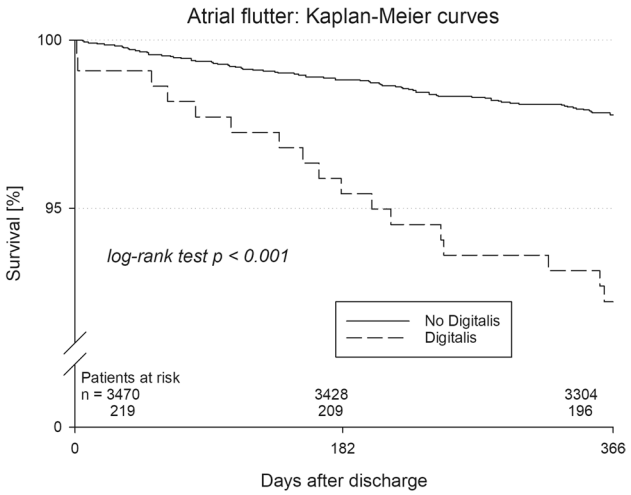

Fig. 1 Kaplan–Meier curves for mortality in patients undergoing ablation of atrial flutter with and without digitalis therapy

Subgroup analyses

Two subgroup analyses were performed to better understand the negative effects of digitalis therapy. First, the present data were separately examined for patients undergoing ablation of atrial flutter, AF, or focal atrial tachycardia. Of note, an increased mortality was in particular observed for patients undergoing ablation of atrial flutter (7.8% vs. 2.2%, $p<0.001$, Fig. 3) or focal atrial tachycardia (14.3% vs. 2.4%, $p=0.007$), although the number of patients undergoing ablation of the latter was rather low. No significant differences were observed for patients undergoing ablation for AF (Fig. 4).

Of note, in a subgroup of patients with heart failure defined as a significantly impaired left ventricular function (left ventricular ejection fraction < 40%) and symptomatic heart failure (NYHA II or worse), a significantly increased 1-year mortality was observed in patients with digitalis (14.5% vs. 4.9%, $p=0.003$). Again, this difference was based on significant differences in patients undergoing ablation of atrial flutter, while no significant differences were observed in the other two entities (5).

Discussion

The present study delivers 'real-world' data on the clinical use of digitalis glycosides in patients undergoing catheter ablation of supraventricular arrhythmias. The proportion of

Table 4 In-hospital complications and complications during follow-up (MACE = death, myocardial infarction, MACCE = death, myocardial infarction, and stroke)

	Digitalis group ($n=417$)	Control group ($n=8191$)	Odds ratio (95%-confidence interval)
In-hospital complications			
Non-fatal myocardial infarction	0% ($n=0$)	0% ($n=0$)	–
Non-fatal stroke	0.2% ($n=1$)	0.1% ($n=9$)	2.19 (0.28–17.29)
Non-fatal major bleeding	0.2% ($n=1$)	0.5% ($n=44$)	0.45 (0.06–3.24)
Complications during follow-up			
Mortality[a]	4.7% (KM)	1.3% (KM)	3.54 (2.18–5.77)
MACE (death or MI)[a]	4.7% (KM)	1.6% (KM)	3.01 (1.86–4.87)
MACCE (death, MI or stroke)[a]	5.4% (KM)	2.2% (KM)	2.54 (1.63–3.96)
Non-fatal major bleeding	2.0% ($n=7$)	0.9% ($n=69$)	2.22 (1.01–4.86)
Arrhythmia recurrence among survivors	37.1% ($n=135$)	36.4% ($n=2812$)	1.03 (0.83–1.28)

[a]Kaplan–Meier (KM) estimates at 366 days after index discharge

Table 5 Baseline patient characteristics in patients with digitalis therapy and the propensity-matched (weighted) control group

	Digitalis therapy	Weighted Control group	Standardized mean difference
Number of patients	$n=417$	$n=418.9$	
Age (years)	66.1 ± 10.1	66.2 ± 10.0	− 0.01
Male (%)	64.7	64.8	− 0.00
LVEF > 50% (%)	58.8	58.8	− 0.00
LVEF < 30% (%)	10.4	10.1	+ 0.01
Coronary artery disease (%)	33.6	33.8	− 0.01
Hypertension (%)[a]	66.7	72.7	− 0.13
Diabetes (%)	25.7	25.7	− 0.00
COPD (%)[a]	9.7	10.2	− 0.02
NYHA class (%) II or worse[b]	60.6	60.3	+ 0.01
Pacemaker (%)	10.6	11.3	− 0.02
ICD (%)	5.8	5.2	+ 0.02
CRT (%)	2.6	2.2	+ 0.03

LVEF left ventricular ejection fraction, *COPD* chronic obstructive pulmonary disease, *ICD* implantable cardioverter/defibrillator, *CRT* cardiac resynchronization therapy

[a]Data available in a subset of patients only

[b]In patients with structural heart disease

Table 6 Cardiovascular medication at time of index discharge in the digitalis group and the propensity-matched (weighted) control group

	Digitalis group	Weighted control group	Standardized mean difference
Number of patients	$n=417$	$n=418.9$	
ACE-inhibitor/AT1 receptor antagonist	67.9%	68.2%	− 0.01
Betablocker	85.6%	86.1%	− 0.01
Diuretics	55.2%	55.4	− 0.00
Class-I antiarrhythmic drugs	8.4%	8.4%	+ 0.00
Class-III antiarrhythmic drugs	16.1%	16.5	− 0.01
Class-IV antiarrhythmic drugs	5.8%	6.1%	− 0.02
Statin	46.5%	46.8	− 0.00

patients receiving digitalis glycosides is rather low. Digitalis therapy was associated with poorer prognosis regarding death from any cause as well as severe clinical events including myocardial infarction, death, or major bleeding. This accounts in particular for patients undergoing ablation of atrial flutter or focal atrial tachycardia, while mortality was generally low in patients undergoing ablation of AF. However, analysis of important clinical parameters suggests that the incidence of comorbidities with impact on overall prognosis is significantly elevated in the population receiving digitalis glycosides.

Patient collective and demographics

The present patient cohort represents a typical collective of patients with mainly atrial flutter or atrial fibrillation. Of note, important differences between digitalis-treated and patients without digitalis therapy were observed. Important factors such as age, cardiovascular disease including myocardial infarction, impaired left ventricular function, and clinical heart failure were significantly increased in digitalis-treated patients. In addition, the prevalence of pacemaker and defibrillator systems was also increased in digitalis-treated patients. In the current ESC recommendations, digitalis is suggested for acute rate control in combination with beta-blockers. In addition, digitalis can also be considered for long-term rate control [2]. Some older studies including the digitalis investigation group (DIG) trial displayed that digitalis did not affect overall mortality, but led to an important reduction of hospitalizations [15, 16]. In contrast, other trials reported an increased mortality in patients treated with digoxin [17–19]. However, these effects have not been attributed to digitalis treatment itself but to selection and prescription bias [2]. In a post hoc propensity-matched analysis of the AFFIRM trial, no evidence of increased mortality or hospitalization was reported in patients taking digoxin as

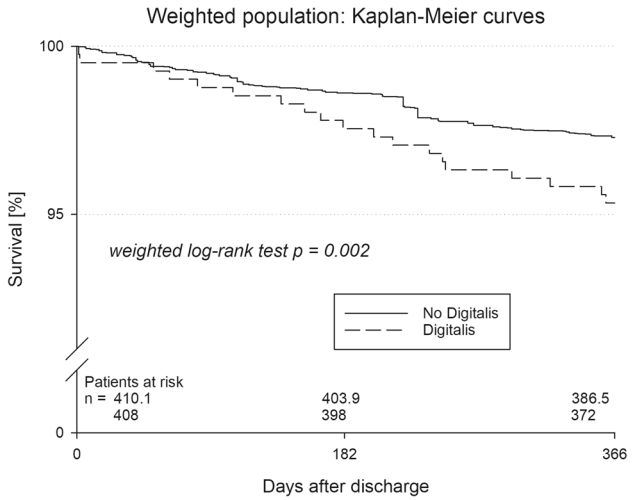

Fig. 2 Kaplan–Meier curves for mortality in patients undergoing ablation of atrial flutter, atrial fibrillation, or focal atrial tachycardia with digitalis therapy and in the propensity-matched (weighted) population without digitalis therapy

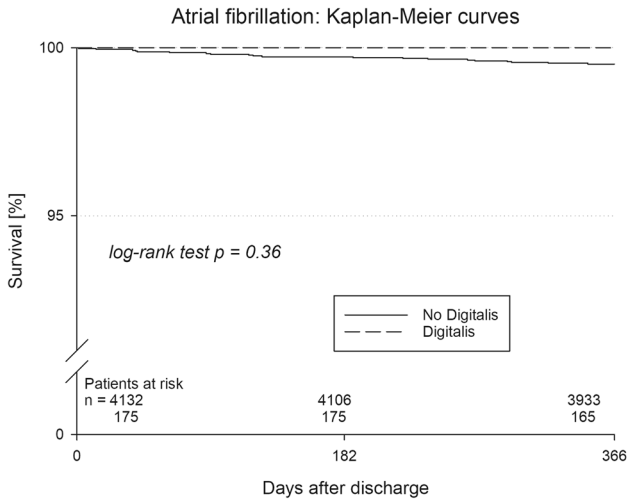

Fig. 3 Kaplan–Meier curves for mortality in patients undergoing ablation of atrial fibrillation with and without digitalis therapy

baseline initial therapy [20]. Of note, the guidelines note that digitalis in general may be prescribed to sicker patients [2, 21].

Procedural data and follow-up

Regarding the ablation procedure ablation failure was more frequently reported in patients exposed to digitalis therapy. This aspect may be due to the fact that patients receiving digitalis presented more severe comorbidity that may have impaired the ablation procedure and the increased rate of long-lasting arrhythmias reducing the probability of success. As a result, digitalis therapy may have been prescribed for rate control. This is also reflected in the prescription rate of antiarrhythmic agents which is higher in patients without digitalis therapy as well as in the administration of heart failure medication which is significantly higher in digitalis-treated patients.

In the present analysis, a significantly increased mortality after a follow-up duration of 1 year was observed for digitalis-treated patients undergoing ablation of atrial flutter or focal atrial tachycardia but not for patients undergoing ablation of AF. Major bleedings have also occurred more frequently in the digitalis group reflecting the fact that digitalis-treated patients presented more severe comorbidities and were significantly older. Furthermore, hospitalizations were reported more often for digitalis-treated patients. These results underline the impression from the previous trials, where an association between an adverse outcome and digitalis therapy was reported. The observed association of digitalis treatment with increased mortality in patients undergoing ablation of atrial flutter may reflect the fact that rate control in atrial flutter often is not effective. As a result, digitalis treatment should be avoided in atrial flutter.

Subgroup analyses of the ROCKET AF and ENGAGE AF-TIMI 48 trials displayed a significant elevation of all-cause mortality and sudden cardiac death in patients receiving digitalis glycosides and suffering from atrial fibrillation with and without heart failure [22, 23]. Furthermore, a meta-analysis has underlined that an increase of mortality is also found in heart failure patients without atrial fibrillation [24]. In addition, a post hoc digoxin subgroup analysis of the ARISTOTLE

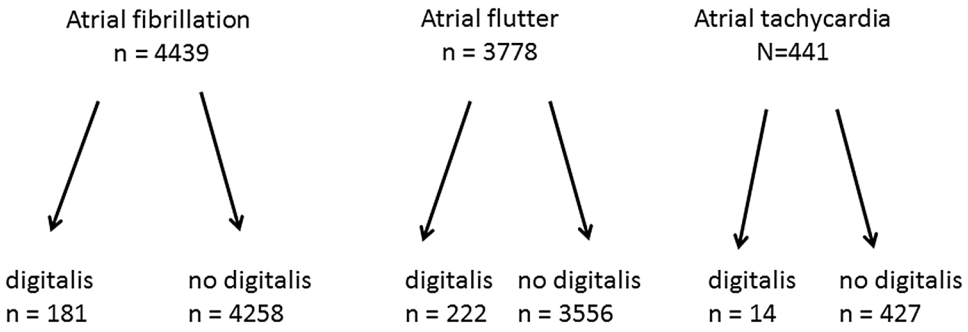

Fig. 4 Distribution of patients in study subgroups

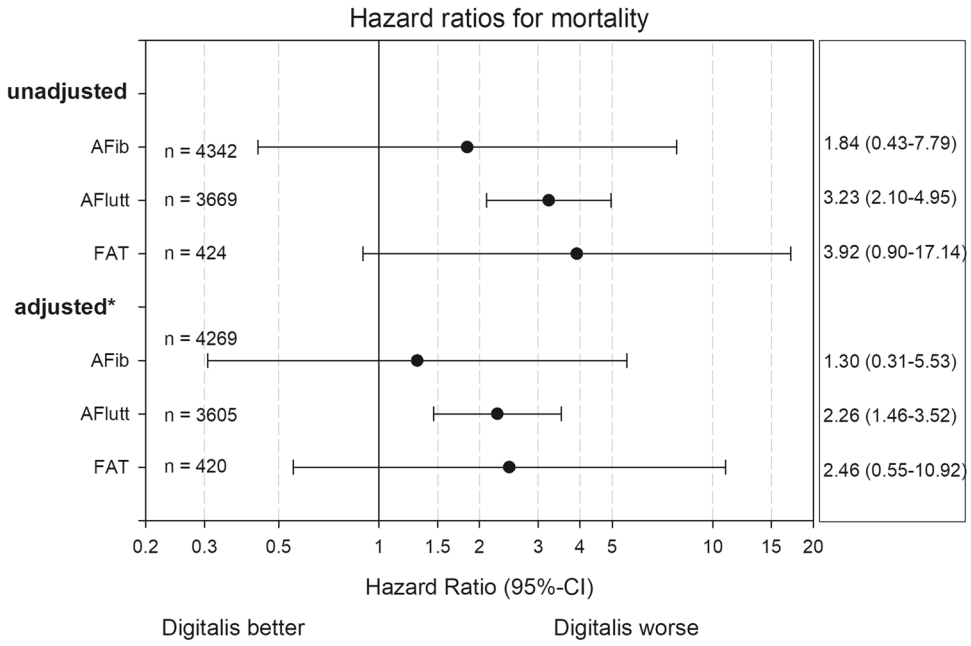

Fig. 5 Hazard ratios for mortality. Unadjusted (top) and adjusted for age (linear), sex, heart failure with reduced ejection fraction (HFrEF, EF ≤ 40%, and NYHA II+) and diabetes

trial suggested that the risk of death was associated with higher serum digoxin concentrations [25]. Most important, this effect was only reported for high digoxin concentrations of 1.2 ng/ml and above supporting the previously published data from the DIG trial [15, 25].

The exact reasons for the increased mortality of digitalis-treated patients cannot be determined as only an association between increased mortality and digitalis treatment has been shown. This also accounts for the observed increased bleeding risk in digitalis-treated patients. Of course, in all cited studies, digitalis-treated patients presented more comorbidities and a higher prevalence of factors relevant for clinical outcome. Therefore, a certain bias is most likely. The described effect was preserved after adjustment for important risk factors such as age, heart failure, and diabetes, although this of course does not exclude a treatment bias [21, 26, 27]. Furthermore, experimental data have suggested that digitalis therapy may also have direct deleterious effects. For example, a combination with other, in particular antiarrhythmic agents, may have negative effects. In this context, deleterious effects have been observed for the combination of dronedarone and digitalis glycosides in both healthy and failing rabbit hearts [6], supporting the results of the PALLAS trial, where this association was also found [4]. However, the employment of ouabain instead of clinically available digitalis glycosides limits the transferability to the clinical setting.

Limitations

As the present data are derived from a registry important limitations apply. The design of the registry most likely includes a selection bias, since patient selection cannot be as precise as in randomized clinical trials and the prescription of digitalis most likely depended on relevant comorbidities and additional undocumented factors. Of note, treatment with digoxin or digitoxin was not differentiated in the German Ablation Registry. Unfortunately, information on serum concentrations was not obtained in this registry. Thorough data about medical treatment before the ablation procedure are also not available. In addition, analysis of complementary data is not as thorough compared with randomized trials. The results of the present analysis should be interpreted in a descriptive sense. Furthermore, the follow-up duration of 1 year is rather short. This aspect is due to the design of the German Ablation Registry. In addition, arrhythmia recurrence has only been reported as a fixed item at the discretion of the operator and was not further specified. Nonetheless, the results of this study represent 'real-life' data on patients receiving digitalis therapy who undergo catheter ablation and delivers important insights on these patients and their outcome.

Conclusion

In the present study, an association with increased mortality and an increased rate of other severe adverse events was observed in patients undergoing catheter ablation of atrial flutter or focal atrial tachycardia but not in patients undergoing ablation of AF. This effect was preserved after adjustment for relevant risk factors. The results from this 'real-life' registry are consistent with previously published clinical and experimental studies, where similar trends were described. However, whether digitalis therapy promotes a poorer prognosis or may just serve as a marker for this aspect cannot be thoroughly interpreted from the results of this registry and previous studies. Nonetheless, it may be stated that the presence of digitalis therapy may indicate more severe comorbidities as well as a limited perspective for rhythm control.

Compliance with ethical standards

Conflict of interest D.T. reports receiving lecture fees/honoraria from Bayer Vital, Boehringer Ingelheim Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Pfizer Pharma, Sanofi-Aventis, St. Jude Medical and ZOLL CMS. T.L. reports modest speaker honoraria from Medtronic, Biotronik and Boston Scientific. All the other authors declared no conflict of interest related to this study.

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