Digitalis Therapy in Patients With Ventricular Tachyarrhythmias

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Research Article

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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 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 outcome was all-cause mortality at three years, secondary endpoints comprised of a composite arrhythmic endpoint (i.e., recurrences of ventricular tachyarrhythmias, sudden cardiac death) and cardiac rehospitalization. Kaplan Meier, multivariable cox regression and time trend analyses were applied for statistics.

Results: A total of 831 patients were included (20% treated with digitalis and 80% without). At three years, digitalis treatment was not associated with all-cause mortality in patients with ventricular tachyarrhythmias (24% vs. 21%, log rank p=0.736; HR=1.063; 95% CI 0.746-1.515; p=0.736). However, digitalis therapy was associated with increased risk of the composite endpoint (38% vs. 23%; log rank p=0.001; HR=1.719; 95% CI 1.279-2.311; p=0.001) and cardiac rehospitalization (31% vs. 18%; log rank p=0.001; HR=1.829; 95% CI 1.318-2.538; p=0.001) at three years, which was still evident within multivariable Cox regression analyses. Finally, digitoxin was associated with worse prognosis than digoxin.

Conclusion: Digitalis therapy was not associated mortality in patients with ventricular tachyarrhythmias, but with increased risk of the composite arrhythmic endpoint and cardiac rehospitalization at three years.

Introduction

For symptomatic treatment of systolic heart failure (HF), digitalis glycosides have been used for over 230 years to improve patients' symptoms, whereas heterogenous 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 significant reduction of mortality, but showed decreased risk of rehospitalization as compared to patients treated with 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 heart failure, respectively a class IIa indication for rate control in AF patients.(5, 6) This led to decreased prescription rates over the past decades.(7, 8) In contrast, many observational studies suggested adverse outcomes in patients treated with digitalis as compared to those without.(2, 3, 9) For instance, a meta-analysis including 19 studies and over 300,000 patients reported 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 increased risk of arrhythmic events. However, data focusing on the risk of arrhythmic endpoints in patients treated with digitalis, predominantly focus on patients undergoing implantation of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death.(10, 11)

To the best of our knowledge, there is no data available whether digitalis affects long-term outcomes of consecutive patients with ventricular tachyarrhythmias. Therefore, this study evaluates the prognostic impact of digitalis therapy on the primary endpoint all-cause mortality, as well as on secondary endpoints (i.e, composite endpoint, cardiac rehospitalization) in consecutive patients with ventricular tachyarrhythmias with HF and/or AF despite beta-blocker therapy. Furthermore, prognosis of patients treated with digoxin is compared to those treated with digitoxin. Finally, time trend analyses were performed regarding prescription rates of digitalis during the study period (2002 until 2015).

Methods

Data collection and documentation

The present study included retrospectively all patients surviving index episodes of ventricular tachyarrhythmias (i.e., ventricular tachycardia (VT) and ventricular fibrillation (VF)) on admission from 2002 until 2016 at our institution as recently published.(12) 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 tachyarrhythmias 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.

Inclusion and exclusion criteria

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

Decision to treat patients with beta-blocker and digitalis was based on the discretion of the cardiologists during routine care according to European guidelines.(5, 6, 13, 14) 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 or 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 three years for all outcomes. The primary prognostic endpoint was all-cause mortality. All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices (“bureau of mortality statistics”) 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, sudden cardiac death) and cardiac rehospitalization. Cardiac rehospitalization comprised of rehospitalization due to VT, VF, acute myocardial infarction (AMI), acute heart failure and inappropriate device therapy.

Statistical methods

Quantitative data are presentedas mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution ofthe 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 Gaussiandistribution were tested by the Kolmogorov-Smirnov test. Spearman’s rank correlationfor nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies and compared using the Chi^2 test or the Fisher’s exact test, as appropriate.

Firstly, 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 ($p<0.05$) 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), acute myocardial infarction (AMI), AF, LVEF <35%, the presence of an ICD and digitalis therapy. Thereafter, 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. Chi^2 test was applied to compare frequencies of digitalis prescription rates.

The result of a statistical test was considered significant for 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, New York) were used for statistics.

Results

Study population

From a total of 2,422 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 of 831 patients with HF (79%), AF (50%), of which 29% revealed both entities. Within the entire study cohort, 20% of all patients were treated with digitalis and 80% without (p=0.001). Target dosages were reached already 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 in patients with and without digitalis treatment (71-78% vs. 22-29%; p=0.073). The overall rates of HF (i.e., LVEF < 45%) were comparable between digitalis and non-digitalis (79% vs. 80%; p=0.646), whereas significantly more digitalis patients suffered from AF (62% vs. 47%; p=0.001). Cardiovascular risk factors were equally distributed within both groups, despite a higher rate of hyperlipidaemia in patients with digitalis treatment (45% vs. 36%; p=0.040). Especially the rates and extend of coronary artery disease and the rate of chronic kidney disease were similar in both groups, whereas more patients with digitalis therapy had a LVEF < 35% (68% vs. 52%; p=0.003). In contrast, concomitant pharmacological treatment regarding angiotensin converting enzyme inhibitors (ACEi), receptor blockers (ARB) and amiodarone were comparable.

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

Median follow-up time within the entire study cohort was 4.0 years (IQR 1.7 – 7.5 years). At three years of follow-up, the primary endpoint all-cause mortality occurred in 24% of the patients with digitalis treatment and in 21% without. Accordingly, risk of all-cause mortality was not affected by treatment with digitalis (log rank p=0.736; HR=1.063; 95% CI 0.746-1.515; p=0.736) **(Table 2 and Figure 2, left panel).** In contrast, digitalis was associated with the composite endpoint (38% vs. 23%; log rank p=0.001; HR=1.719; 95% CI 1.279-2.311; p=0.001) and the risk of cardiac rehospitalization at three years (31% vs. 18%; log rank p=0.001; HR=1.829; 95% CI 1.318-2.538; p=0.001) **(Figure 2, middle and right panel).**

Stratification by atrial fibrillation and heart failure

Characteristics of patients, stratified by AF and HF, are presented within **Table 3**. In AF patients (n=415), VT was more common in patients treated with digitalis than in patients without (80% vs. 70%; p=0.041). In line, LVEF < 35% was more common in AF patients on digitalis treatment (61% vs. 44%; p=0.025). In patients with AF, digitalis use was not associated with the primary endpoint of all-cause mortality at three

years (27% vs. 24%; log rank p=0.963; HR=1.011; 95% CI 0.651-1.568; p=0.963) **(Figure 3A, left panel).** The composite endpoint (38% vs. 20%; log rank p=0.001; HR=1.957; 95% CI 1.312-2.917; p=0.001) and rehospitalization (31% vs. 18%; log rank p=0.005; HR=1.837; 95% CI 1.190-2.837; p=0.006) were more common in patients treated with digitalis **(Figure 3A, middle and right panel)**.

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=0.956), the composite endpoint (39% vs. 25%; log rank p=0.003; HR=1.620; 95% CI 1.174-2.234; p=0.003) and cardiac rehospitalization (36% vs. 20%; log rank p=0.001; HR=1.945; 95% CI 1.382-2.737; p=0.001) **(Figure 3B).**

Subsequently, patients with the combination of AF and HF (n=242) were analyzed. In patients with AF and HF, all-cause mortality at three years was comparable among patients with and without digitalis treatment (26% vs. 26%; log rank p=0.617; HR=0.869; 95% CI 0.502-1.505; p=0.617). In contrast, digitalis therapy increased the risk of the composite endpoint (41% vs. 24%; log rank p=0.028; HR=1.688; 95% CI 1.052-2.710; p=0.030) and cardiac rehospitalization (41% vs. 24%; log rank p=0.013; HR=1.810; 95% CI 1.125-2.915; p=0.015) at three years **(Figure 3C).**

Multivariable cox regression models

After multivariable adjustment, digitalis was not associated the risk of all-cause mortality at three years (HR=0.982; 95% CI 0.663-1.453; p=0.927) (**Table 4**). In contrast, increasing age (HR=1.039; p=0.001), presence of diabetes mellitus (HR=1.763; p=0.001), chronic kidney disease (HR=1.583; p=0.004) and LVEF <35% (HR=1.651; p=0.004) were associated with impaired prognosis, whereas an ICD was associated with decreased long-term mortality (HR=0.438; p=0.001). Finally, the risk of the composite endpoint (HR=1.412; 95% CI 1.025-1.946; p=0.035) and the risk of cardiac rehospitalization (HR=1.561; 95% CI 1.101-2.215; p=0.012) were increased in patients treated with digitalis as compared to those without (**Table 4**).

Prognostic impact of digoxin versus digitoxin treatment

Within the entire study cohort, 63% of patients with digitalis were treated with digoxin and 37% with digitoxin. At three years of follow-up, treatment with digitoxin was associated with worse long-term survival as compared to digoxin (38% vs. 15%; log rank p=0.001; HR=3.033; 95% CI 1.600-5.752; p=0.001) (**Figure 4**). Adverse prognosis was still evident after multivariable Cox regression analysis (HR=1.988; 95% CI 0.952-4.154; p=0.068; statistical trend) (not shown). In contrast, secondary endpoints were not affected by type of digitalis treatment (i.e., digoxin vs. digitoxin).

Time trend analyses

Finally, we investigated whether digitalis treatment has changed during 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=0.001 for the trend). This trend was observed in both patients with AF (i.e., 53.8% to 7.7%; p=0.001) and HF (i.e., 46.4% to 6.7%; p=0.001) (**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, sudden cardiac death) and cardiac rehospitalization at three years in patients surviving index episodes of ventricular tachyarrhythmias.

During the study period from 2002 until 2015, treatment with digitalis has decreased from 46.9% to 7.5%. This trend was observed both in patients suffering from AF and HF. The present study suggests digitalis treatment (digoxin in 67% and digitoxin in 37%) is not associated with 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 there are many observational studies 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 weather digitalis is more likely prescribed for patients with more advanced stages of cardiovascular disease, who have *per se* impaired long-term prognosis.(15, 16) Besides studies focusing on AF and/or HF, limited data is available focusing on patients with high risk for ventricular tachyarrhythmias, although it is well known that digitalis treatment increase the chance arrhythmias due to oscillatory afterpotentials and cardiac automacity.(17) Erath *et al.* included 1,020 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 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.(9) 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 increased risk of the composite arrhythmic endpoint, which was still significant after multivariable adjustment, and which was demonstrated within all analyzed subgroups. In line, 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 increased risk of appropriate ICD therapy. Besides digitalis treatment, low LVEF and history of non-sustained VT decreased freedom from appropriate ICD therapy.(10) Similar observations, suggesting impaired prognosis in patients treated with digitalis were made by Stein *et al.*, including 1,703 ICD patients at one year of follow-up.(11) Whereas most studies focused on the prognostic value of digoxin rather than digitoxin, comparisons of both digitalis glycosides are rare until now. However, comparable outcomes of patients treated with digoxin and digitoxin were observed within the ICD cohort of Erath *et*

al..(9) Our study however, found 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, risk of arrhythmic endpoints are affected by multiple pharmacotherapies, especially beta-blockers and amiodarone.(18) Thus, it was recently demonstrated that beta-blockers reduce the risk of ventricular tachycardias leading to syncope's within 226 ICD recipients.(19) To decrease the chance of possible selection bias caused by heterogenous 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.(9, 11) Wheatear digitalis therapy itself increases the risk of arrhythmic events in patients with ventricular tachyarrhythmias or wheatear patients on digitalis have increased risk of arrhythmic events due to increased severity of cardiovascular disease needs to be investigated within further RCT.

In conclusion, this study demonstrates that treatment with digitalis has significantly decreased during the past decade (i.e., 46.9% to 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, risk of the composite endpoint and cardiac rehospitalization were 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, digitoxin may be associated with even worse prognosis as compared to digoxin.

Study limitations

This observational and retrospective registry-based analysis reflects a realistic picture of consecutive health-care supply of high-risk patients presenting with ventricular tachyarrhythmias. Lost to follow-up rate regarding the evaluated endpoint of all-cause mortality was minimal. Pharmacological therapies were based on discharge medication at index event. Despite multivariable adjustment a certain prognostic impact of comorbidities in the digitalis group may not be excluded. All clinical data was documented reliably by individual cardiologists during routine clinical care being blinded to final analyses, alleviating the use of an independent clinical event committee. Unmeasured cofounding (including degree of AF or HF symptoms) may also affect our results, which may predominantly be present in digitalis patients. The present results need to be re-evaluated within even larger and more representative multi-centre registry data or even randomized controlled trials, especially focusing on the effect of digitalis in AF patients controlling for cofounding AF symptoms.

Declarations

Ethics approval and consent to participate

This study is based on a retrospective data analysis/registry and has been approved by the local ethics commission II of the faculty of Medicine Mannheim, University of Heidelberg, where no informed consent

was deemed necessary for this study (ethical approval number 2016612NMA) (ClinicalTrials.gov identifier: NCT02982473).

Consent for publication

Not applicable.

Availability of data and materials

Data will be made available from the corresponding author on reasonable request.

Competing interests

Not applicable.

Funding

Not applicable.

Authors' contributions

Conceptualization, T.S, I.A., M.B methodology, T.S., S.Z., L.R., M.B.; software, M.Z., M.B.; validation, T.S., M.B.; formal analysis, M.Z..; investigation, T.S., B.K., M.Z.,L.R.,M.A., K.W., K.M., T.B., M.A., I.A., M.B..; resources, T.S., B.K., M.Z.,L.R.,M.A., K.W., K.M., T.B., M.A., I.A., M.B.; data curation, T.S., B.K., M.Z.,L.R.,M.A., K.W., K.M., T.B., M.A., I.A., M.B.; writing—original draft preparation, T.S., M.B..; writing—review and editing, T.S., M.Z.,L.R.,M.A., K.W., K.M., T.B., M.A., I.A., M.B.; visualization, T.S..; supervision, I.A., M.B..; project administration, I.A., K.M., T.B., M.B..; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

Compliance with Ethical Standards

Ethics approval and consent to participate

This study is based on a retrospective data analysis/registry and has been approved by the local ethics commission II of the faculty of Medicine Mannheim, University of Heidelberg, where no informed consent was deemed necessary for this study (ethical approval number 2016612NMA) (ClinicalTrials.gov identifier: NCT02982473).

Disclosure of potential conflicts of interest

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

Research involving Human Participants and/or Animals

Not applicable.

Informed consent

Not applicable.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

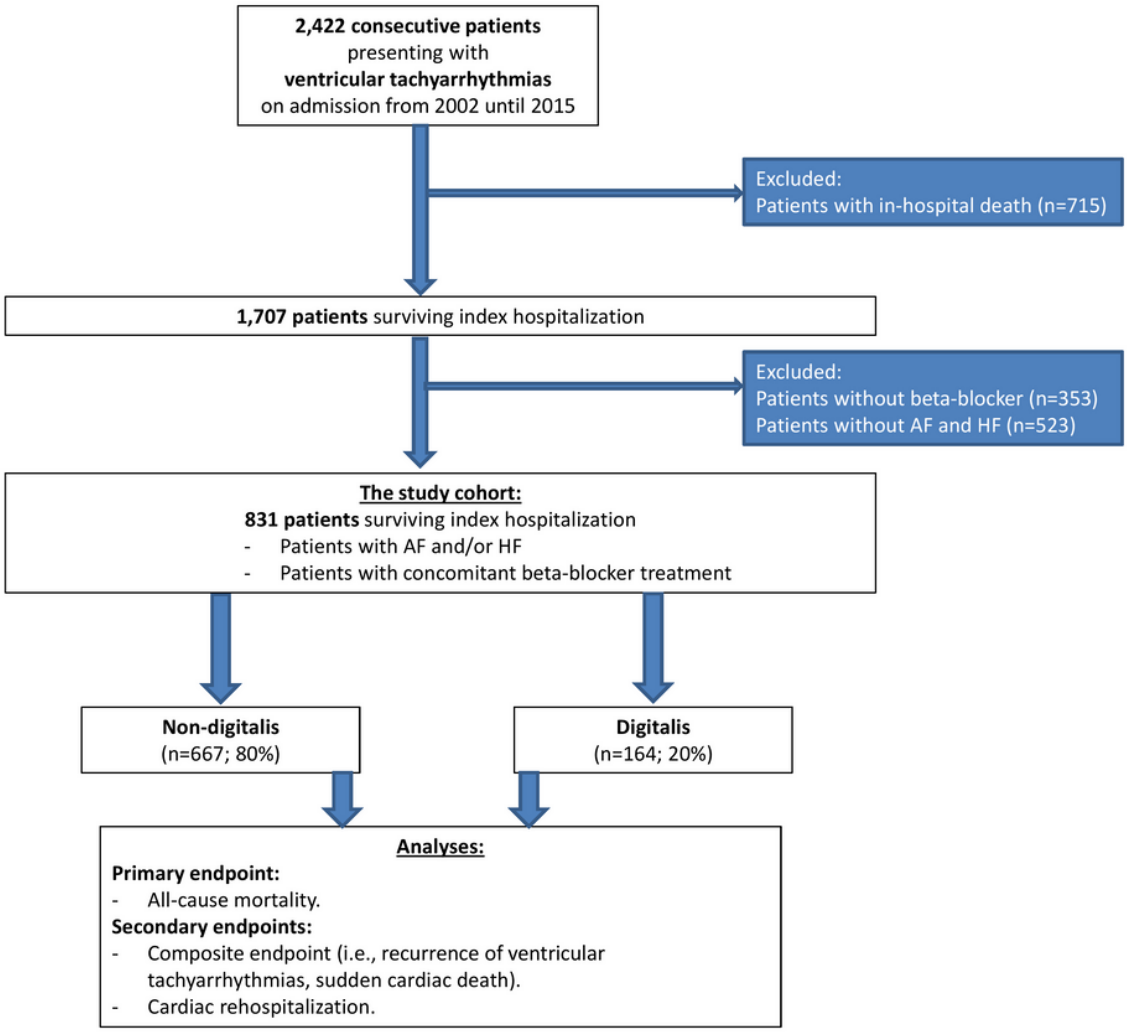

Figure 1

Study flow chart.

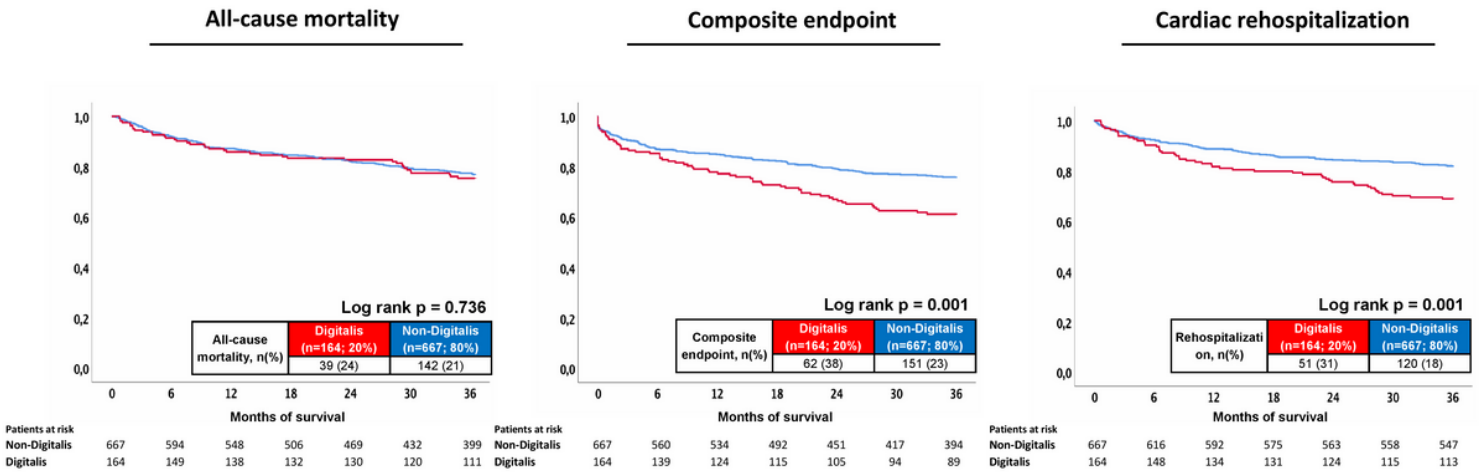

Figure 2

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.

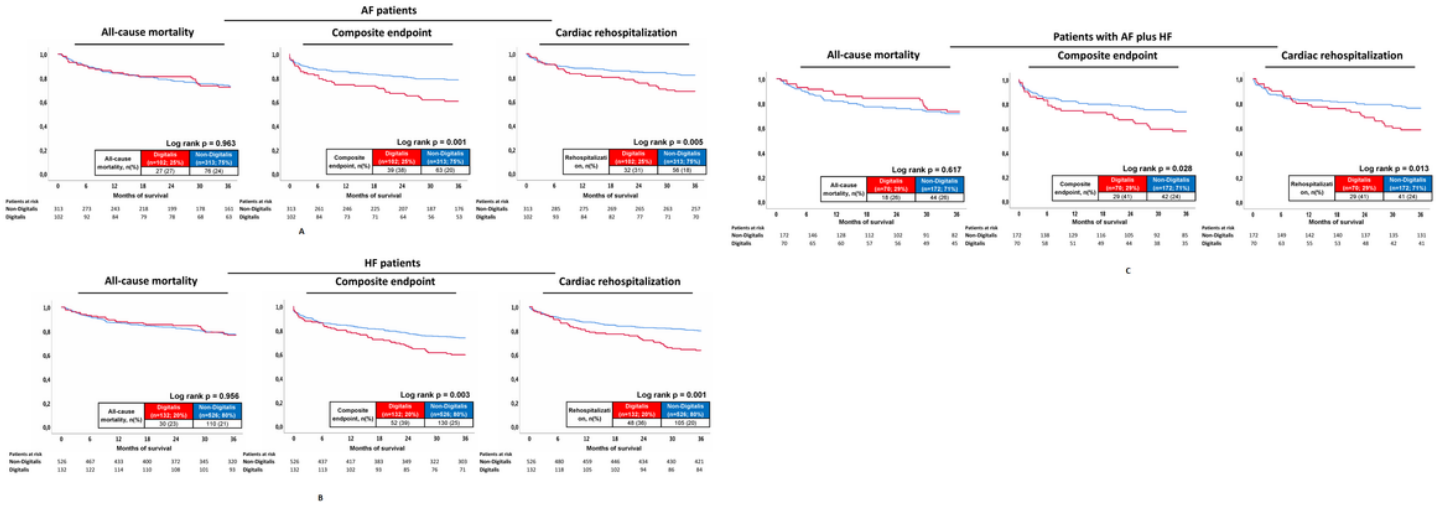

Figure 3

A: 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) in patients with AF. B: 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) in patients with HF. C: 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) in patients with AF and HF.

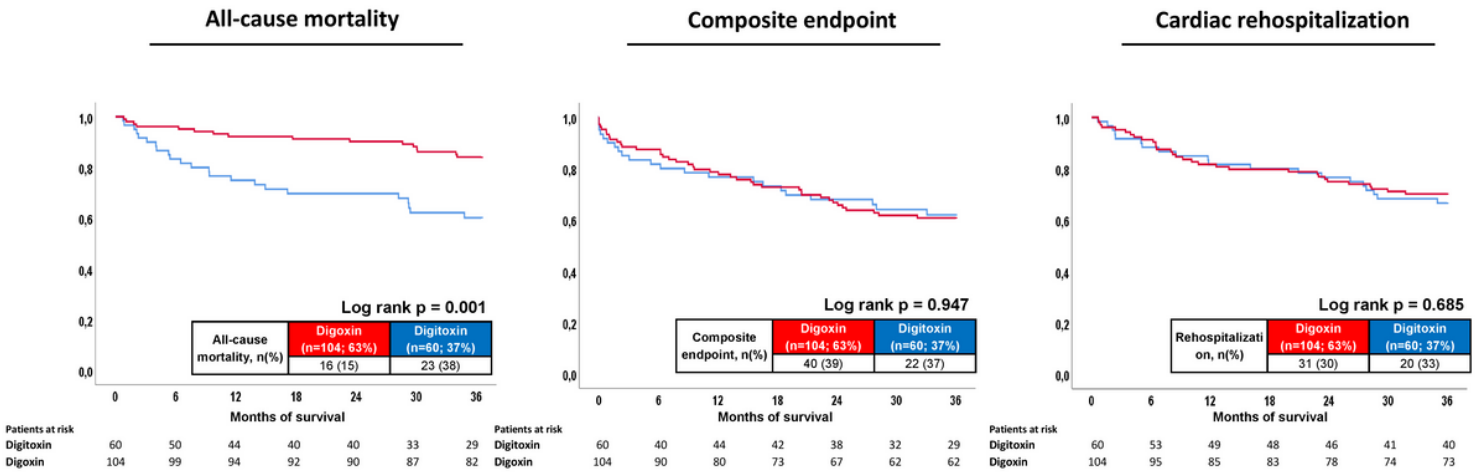

Figure 4

Prognostic impact of digoxin versus digitoxin 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).

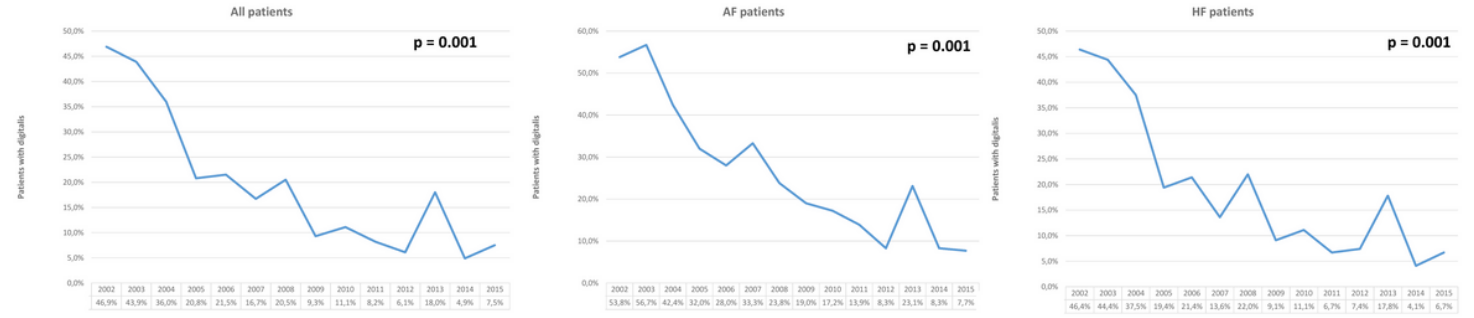

Figure 5

Time trend analyses regarding treatment with digitalis within the entire cohort (left panel), as well as in AF (middle) and HF patients (right).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1DigitalisCharacteristics.pdf
- Table2DigitalisEndpoints.pdf
- Table3DigitalisHFvsAFCharacteristics.pdf
- Table4CoxRegression.pdf