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Digoxin treatment is associated with increased total and cardiovascular mortality in anticoagulated patients with atrial fibrillation

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ABSTRACT

Background: Some evidences suggest that the use of digoxin may be harmful inatrial fibrillation (AF) patients. The aim of the study was to investigate in a "real world" of AF patients receiving vitamin K antagonists (VKAs), the relationship between digoxin use and mortality.
Methods: Prospective single-center observational study including 815 consecutive non-valvular AF patients treated with VKAs. Total mortality was the primary outcome of the study. We also performed a sub-analysis considering only cardiovascular (CV) deaths. Time in therapeutic range (TTR) was used for anticoagulation quality.
Results: Median follow-up was 33.2 months (2460 person-years); 171 (21.0%) patients were taking digoxin. Compared to those without, patients on digoxin were older ($p = 0.007$), with a clinical history of HF ($p < 0.001$) and at higher risk of thromboembolic events ($p < 0.001$). No difference in TTR between the two groups was registered ($p = 0.598$). During the follow-up, 85 deaths occurred: 47 CV and 38 non-CV deaths; 35 deaths occurred in digoxin users (20.6%). A significant increased rate of total mortality was observed in digoxin-treated patients ($p < 0.001$). Multivariable analysis showed that digoxin was associated with total mortality (hazard ratio [HR]: 2.224, $p < 0.001$) and CV death (HR: 4.686, $p < 0.001$). A propensity score-matched analysis confirmed that digoxin was associated with total mortality (HR: 2.073, $p = 0.0263$) and CV death (HR: 4.043, $p = 0.004$).
Conclusions: In AF patients on good anticoagulation control with VKAs, digoxin use was associated with a higher rate of total and CV mortality.

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia requiring medical treatment, and it is known to be associated with an increased risk of stroke and cardiovascular death [1,2].

The management of patients affected by AF is complex, including both anticoagulant treatment for the prevention of thromboembolic complications, and the use of antiarrhythmic drugs to maintain sinus rhythm or achieve a good ventricular heart rate control [3]. An intriguing clinical challenge is the treatment of patients presenting with AF and heart failure (HF). HF is a frequent cardiac disorder associated with AF, and may contribute to worsen prognosis of patients presenting with both conditions [4]. The association between AF and HF is not surprising since these two conditions share similar atherosclerotic risk factors, including arterial hypertension, diabetes, metabolic syndrome and peripheral artery disease [5]. Moreover, the unfavorable hemodynamic consequences of AF such as elevated heart rate, increased cardiac filling pressures and loss of the atrial contribution to ventricular filling, can contribute to impair ventricular function [6].

Digoxin is largely used in HF as it was demonstrated to reduce hospitalization and symptoms in this setting [7]. In AF patients, digoxin has been widely used for heart rate control, particularly in those patients with HF, since it has no negative inotropic effects compared to other antiarrhythmic drugs [8]. The recently published guidelines by the American College of Cardiology/American Heart Association for the management of patients with AF indicate digoxin as effective to control heart rate, alone or in combination with a β-blocker, in patients with AF and HF and reduced ejection fraction (EF), or combined with a non-dihydropyridine calcium channel antagonist (NDCCA), in AF patients with HF and preserved EF [9].

Despite its proved efficacy, there is some evidence to suggest that the use of digoxin may be harmful in patients with AF [10–15], but this finding has not been confirmed [16–20].

To further explore this issue, we sought to investigate, in a prospective cohort of anticoagulated AF patients, if the use of digoxin may increase total mortality, with respect to the presence of HF.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study design and patient selection

This was a prospective single-center study that included 867 consecutive patients with AF who referred to the Atherothrombosis Center of the Department of Internal Medicine and Medical Specialties of "Sapienza" University of Rome from February 2008 to December 2013.

All patients were treated with vitamin K antagonists (VKAs, warfarin/acenocumarol) initially according to $CHADS_2$ score, and afterwards patients were re-classified according to the CHA_2DS_2-VASc score [21]. Anticoagulation therapy was monitored by the International Normalized Ratio, in a therapeutic range of 2.0–3.0. Quality of anticoagulation was evaluated by time in therapeutic range (TTR) according to Rosendaal [22]. All patients with non-valvular AF, aged >18 years of both sexes were included in the study. The following were the exclusion criteria: prosthetic heart valves, severe valve disease, severe cognitive impairment, chronic infectious diseases, autoimmune systemic diseases and active cancer. At baseline, all patients provided a written informed consent. During the first visit, patient's medical history and anthropometric data were recorded. A standard 12-lead electrocardiogram was also performed. Patients presenting with electrocardiographic signs of digoxin overdose at baseline were also excluded.

Cardiovascular risk factors were defined as follows: (i) Arterial hypertension: repeatedly elevated blood pressure (≥140/≥90 mm Hg) or taking antihypertensive-drugs [23]; (ii) diabetes mellitus: a casual plasma glucose ≥200 mg/dl (11.1 mmol/l), or fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l), or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT or taking anti-diabetic drugs [24]; and (iii) heart failure: the presence of signs and symptoms typical of heart failure or reduced ejection fraction (≤40%) [25].

2.2. Outcome events

Total mortality was considered the primary outcome of the study. A sub-analysis considering only CV deaths was also performed. CV death was defined unless an unequivocal non-CV cause of death was confirmed by a central adjudication committee. If a patient died within 4 weeks of stroke or myocardial infarction, this event was recorded as fatal stroke or fatal myocardial infarction. Adjudication of events was performed by two of us (FV, PP), who were blinded to patients' recruitment and clinical and laboratory characteristics of any enrolled patient.

The study protocol was approved by the Sapienza University institutional review board and was conducted in accordance to the declaration of Helsinki [26]. The relationship between digoxin use and outcome events is a secondary outcome of a registered observational prospective study (ClinicalTrials.gov Identifier: NCT01882114).

2.3. Statistical analysis

Categorical variables were reported as counts (percentages); continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR) unless otherwise indicated. Independence of categorical variables was tested by χ^2 test. Normal distribution of parameters was assessed by the Kolmogorov–Smirnov test. Student unpaired t test and Pearson product-moment correlation analysis were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann–Whitney U test and Spearman rank correlation test) were employed for all the other variables.

After dividing the cohort according to the use or not of digoxin, the cumulative risk was estimated using a Kaplan–Meier method for total mortality. The survival curves of the two groups were then formally compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted relative hazards of total mortality by each clinical variable. The multivariate analysis was determined with a forward stepwise variable selection procedure. The same analyses were then repeated in the subset of patients who experienced CV death.

In order to mimic a randomized study and approximate a causal effect estimate, we balanced groups through matching. Propensity scores for the receipt of digoxin for each patient were estimated based on the baseline variables in Table 1 of Supplementary material. Note that these can also be considered as proxies of correlated baseline measurements not used or not available. A greedy matching algorithm was used, finally obtaining a data set of 173 couples of patients. A univariate Cox regression model was then used to estimate hazard ratios on the matched data set. A sensitivity analysis (not reported) showed that final results are reasonably robust with respect to the choice of variables used to build propensity scores. Only p values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (R v3.0.2, R Development Core Team and SPSS v18.0, SPSS Inc.).

The sample size was planned using a log-rank test for comparing mortality rate in patients receiving or not the digoxin. Based on previous reported data, with a median follow-up time of 30 months, assuming a 2 to 1 ratio for number of controls vs. treated patients, an incidence rate of mortality in the control group of 15% and an increase by digoxin of at least 8% we planned a sample size of 783 patients. This guarantees a power of at least 80% at a fixed a type-I error rate of 5%.

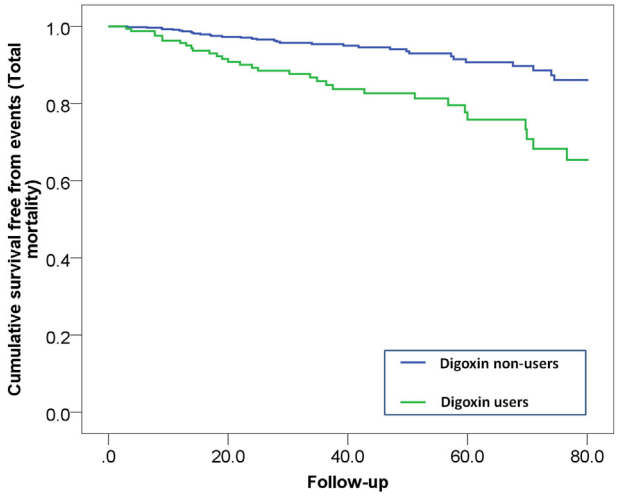

Fig. 1. Kaplan–Meier curve estimates of survival free from total mortality according to the use of digoxin (green line) or not (blue line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results

Based on the above listed exclusion criteria we excluded 52 patients (6.0%); 815 patients were included in the study cohort. All patients were followed for a median time of 33.2 months (IQR: 15.0–53.9) yielding 2460 person-years of observation. Table 1 reports baseline clinical characteristics of the entire cohort.

Mean age was 73.0 ± 8.5 years, 42.6% of patients were females and 55.4% had persistent/permanent AF. Mean CHA_2DS_2-VASc score was 3.5 ± 1.5 and patients were on good anticoagulation control (mean TTR 65.5 ± 17.9%). Patients had paroxysmal in 42.6%, persistent in 8.2%, and permanent in 49.2%. Patients had a clinical history of stroke/TIA in 15.6% and MI/coronary heart disease (CHD) in 22.7%. A history of HF was present in 16.3% of patients. At echocardiographic evaluation, the median EF in the whole cohort was 55.0% [50.0–59.0]; AF patients with HF had an EF of 40.0% [37.0–45.7] compared to 55.0% [50.0–60.0] of patients without HF ($p < 0.001$).

In the whole population, 171 (21.0%) patients were taking digoxin. Of these, 25 (14.6%) were treated with 0.0625 mg, 132 (77.2%) with 0.125 mg, and 14 (8.2%) with 0.250 mg of digoxin. Patients using digoxin were older (74.4 ± 7.2 vs. 72.6 ± 8.8 years, $p = 0.007$), with a clinical history of HF (25.9 vs. 13.7%, $p < 0.001$) and reduced EF (51.3 ± 9.8 vs. 53.5 ± 8.3%, $p = 0.010$) compared to those without. Moreover, they were at higher risk of thromboembolic events (median CHA_2DS_2-VASc score 3 [2–4] vs. 4 [3–5] $p = 0.001$), whilst no difference between the

Table 1
Baseline characteristics of the whole population and according to the use of digoxin.

	Overall (n = 815)	Digoxin use		p value
		No (n = 644)	Yes (n = 171)	
Age (years)	73.0 ± 8.5	72.6 ± 8.8	74.4 ± 7.2	0.007
Female gender (%)	42.6	41.5	46.8	0.224
Permanent AF (%)	49.2	43.2	71.9	<0.001
CHA_2DS_2-VASc score	3 [3–5]	3 [2–4]	4 [3–5]	0.001
TTR (%)	65.5 ± 17.9	65.7 ± 17.9	64.6 ± 17.8	0.598
Hypertension (%)	88.7	88.2	90.6	0.417
Diabetes mellitus (%)	20.2	19.4	23.4	0.284
Heart failure (%)	16.4	13.7	25.9	<0.001
History of stroke/TIA (%)	15.6	15.1	17.5	0.477
History of MI/CHD (%)	22.7	21.8	26.3	0.218
Anti-platelet drugs (%)	8.0	7.9	8.2	0.875
ACE inhibitor/ARBs (%)	69.8	70.0	69.0	0.851
β blockers (%)	40.8	40.7	40.9	1.000
Verapamil (%)	11.9	9.8	19.9	0.001
Statins (%)	41.5	42.6	37.4	0.256
Amiodarone (%)	27.3	31.9	9.9	<0.001

TTR: time in therapeutic range, EF: ejection fraction, TIA: transient ischemic attack, MI: myocardial infarction, CHD: coronary heart disease, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers.

two groups in TTR was observed (64.6 ± 17.8 vs. 65.7 ± 17.9%, p = 0.598). Patients on digoxin had more frequently persistent/permanent AF compared to those not on digoxin (79.3 vs. 48.9%, p < 0.001). Concomitant verapamil use was more frequent in digoxin group (19.9% vs. 9.8%, p = 0.001), whereas the use of amiodarone was more frequent in patients not receiving digoxin (9.9 vs. 31.9%, p < 0.001).

3.1. Total mortality

During the follow-up, 85 deaths occurred. Of these, 47 were CV deaths: 6 fatal MI, 3 fatal ischemic stroke, 38 vascular death (13 progressive HF, 12 ventricular arrhythmia/cardiac arrest, 8 sudden death, 2 acute pulmonary edema, 2 pulmonary embolism, 1 ischemic intestinal infarction); and 38 were non-CV deaths (16 related to neoplastic diseases, 5 for complications after prolonged bed rest, 2 acute lung injuries, 2 acute kidney damages, 2 liver cirrhosis, 1 femur fracture, 1 for surgery complications, 9 undetermined causes).

Of these, 35 deaths occurred in digoxin users (20.6%): 28 CV deaths (10 progressive heart failure, 6 ventricular arrhythmia/cardiac arrest, 3 fatal strokes, 2 fatal MI, 2 acute pulmonary edema, 2 pulmonary embolism, 3 sudden death), and 7 non-CV death (all related to cancer). A significant increased rate of total mortality was observed in patients treated with digoxin compared to those not receiving digoxin (Fig. 1, 20.6 vs. 7.8%, log-rank test p < 0.001).

A stepwise multivariable Cox regression analysis showed a direct association between age (hazard ratio [HR]: 1.113, confidence interval [CI] 95% 1.075–1.152, p < 0.001), history of stroke/TIA (HR: 1.726, CI 95% 1.069–2.789, p = 0.026), diabetes (HR: 1.901, CI 95% 1.185–3.049, p = 0.008), digoxin use (HR: 2.224, CI 95% 1.422–3.477, p < 0.001) and total mortality, whilst the use of ACE inhibitors/ARBs (HR: 0.634, CI 95% 0.409–0.983, p = 0.042) was inversely associated with total mortality (after adjustment for gender, arterial hypertension, history of MI/CHD, antiplatelet therapy, beta blockers, verapamil and amiodarone).

Propensity score analysis confirmed results from Cox regression analysis (see Supplementary material).

3.2. CV deaths

A sub-analysis considering only CV death as outcome showed a significant increased rate of events in AF patients treated with digoxin (16.5 vs. 2.9%, log-rank test: p < 0.001) (Fig. 2).

A multivariable Cox regression analysis showed that the use of digoxin (HR: 4.424, CI 95% 2.443–8.011, p < 0.001), age (HR: 1.114, CI 95% 1.062–1.169, p < 0.001), diabetes (HR: 2.302, CI 95% 1.229–4.313, p = 0.009) and history of stroke/TIA (HR: 2.498, CI 95% 1.364–4.575, p = 0.003) independently predicted CV death. Further analysis was performed to investigate if digoxin treatment was associated with CV death independently from concomitant HF. In the whole cohort 134 (16.4%) AF patients had HF. Compared to those without, patients with HF were older (72.7 ± 8.5 vs. 74.5 ± 8.6 years, p = 0.030), had more frequently persistent/permanent AF (52.8 vs. 69.4%, p = 0.001), higher thromboembolic risk (CHA_2DS_2-VASc score 3 [2–4] vs. 5 [4–6], p < 0.001), and a clinical history more complicated by MI/CHD (18.6 vs. 43.9, p < 0.001). Digoxin was prescribed more frequently in patients with HF compared to those without (33.3 vs. 18.6%, p < 0.001). The quality of anticoagulation, although good, was significantly lower in patients with HF, with a mean TTR of 61.5% (±18.1) compared to 66.2% (±17.8) in patients without HF (p = 0.029).

Digoxin remained associated with CV death both in patients with (HR: 4.463, CI 95% 1.541–12.930, p = 0.006) as well as in those without HF (HR: 4.056, CI 95% 1.965–8.375, p < 0.001).

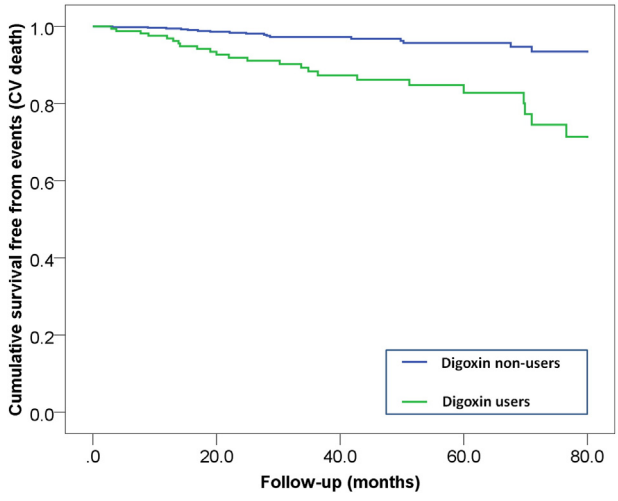

Fig. 2. Kaplan–Meier curve estimates of survival free from CV death according to the use of digoxin (green line) or not (blue line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Our study shows that in a "real world" cohort of AF patients on good anticoagulation treatment, the use of digoxin is associated with an increased risk of total mortality. This finding is likely to be attributed to the increased CV death in digoxin-treated AF patients, and persisted after propensity score analysis.

Digoxin is widely used in AF patients for its efficacy to control heart rate at rest, alone or in combination with other antiarrhythmic agents both in acute and chronic setting.

Digoxin treatment for AF patients with HF has been deduced from the DIG trial [7], in which digoxin was able to reduce hospitalization rate and symptoms of HF. In the last few years, observational trials reported on the impact of treatment digoxin on clinical outcomes in AF patients [10–20].

Thus, analysis from the large Registry of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKSHIA) study on AF patients with and without HF showed that the long-term treatment with digoxin was associated with 1-year increased all-cause mortality in AF patients without HF [10]. Increase of vascular-related death was also detected in digoxin users of the SPORTIF III and V trials, which included AF patients randomized to receive ximelagatran or warfarin for the prevention of thromboembolism [12].

In contrast with these results, the Stockholm Cohort study of Atrial Fibrillation (SCAF), a prospective study on AF patients followed for a mean of 4.6 years, found a neutral effect of digoxin on all-cause mortality and major cardiovascular events [17].

Three recent analyses from the AFFIRM trial, that included 4.060 AF patients [11,16], provided divergent results as an increased CV mortality and all-cause mortality [11], a null effect [16] and an improved survival in AF patients with severe HF were reported in digoxin-treated patients [20].

Furthermore, recent large retrospective analyses from the TREAT-AF trial [13] and two population-based cohorts in Taiwan [14] and Canada [15] showed that digoxin was associated with the risk of death in patients with AF.

In our prospective observational study, conducted on a "real world" population of AF patients on good anticoagulation therapy with VKAs, digoxin treatment increased the risk of total and cardiovascular mortality. Rate of total mortality in previous studies is heterogeneous, ranging from 6.5% to 51% of digoxin-treated patients. In our cohort, 20.6% of AF patients treated with digoxin experienced the primary outcome.

Compared to those digoxin-free, patients taking digoxin were older, with a higher thromboembolic risk and more likely to have HF, which is in accordance with the recommendation for the use of digoxin in AF patients [27].

Our study differs in some aspects from those so far published. This is the first report in which all AF patients were taking oral anticoagulants (OACs), and in which the quality of anticoagulation, expressed by TTR,

was evaluated. In fact, in the SCAF [17] and SPORTIF [12] trial only 50% of patients on digoxin were treated with OACs, and in the AFFIRM trial OAC was mandatory only in the rate control group, whilst in the rhythm group was decided by physicians [3]. This may be a crucial issue since a low anticoagulation quality is associated with an increased rate of cardiovascular event and mortality [28–32]. Thus, in previous works, the excess risk of mortality observed in digoxin-treated AF patients could depend, at least in part, on the fact that patients were receiving a suboptimal anti-thrombotic treatment, such as antiplatelet treatment or no therapy, in some cases. In our study, all patients were treated with OACs, and the anticoagulation control was good, with a mean TTR of 65%, with no differences between the group receiving and not digoxin. Moreover, to corroborate our finding, we performed a propensity-matched analysis, to test if the effect of digoxin was independent from baseline characteristics. We found that digoxin increases the risk of death also after adjustment for baseline clinical characteristics.

Mechanisms through which digoxin increases mortality are not yet clarified [33]. The suggested mechanisms include clinical relevant bradycardia, atrio-ventricular block and ventricular arrhythmias [12]; these arrhythmias may be facilitated by coexistence of electrolyte imbalances (i.e. hypokalemia, hypomagnesemia and hypercalcemia) and/or unrecognized atrio-ventricular accessory pathways [34]. Other putative mechanisms include increased endothelial and platelet activation in AF patients [33], but not in healthy volunteers [35] and activation of baroreceptor function and neuroendocrine system [36,37].

The study has some limitations and implications. The main limitation of the study is represented by the lack of the blood concentration of digoxin, which is associated with cardiac toxicity and increased mortality [38]. Kidney function may affect blood digoxin but we could not provide information regarding it. However, a recent work by Turakhia [13] showed that the increased mortality by digoxin was apparently independent from kidney function. This is an observational single-center study, thus our findings need to be confirmed by a multicenter study with a larger AF cohort. Finally, exposure to digoxin was not included as a time-dependent variable, so this could potentially lead to an underestimation of the risk associated with digoxin use in our population.

Even if we cannot exclude the presence of unidentified confounders, our findings raises concern on the potential harmful effect of digoxin in AF patients, suggesting that the recommendation for its use in this setting should be carefully reconsidered.

In conclusion, anticoagulated AF patients treated with digoxin experience a higher rate of total and cardiovascular mortality compared to those without. Given the lack of a randomized controlled study that would clarify the doubts about the safety of digoxin in patients with AF, the use of digoxin should be carefully considered in this setting.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.11.112.

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