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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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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%.

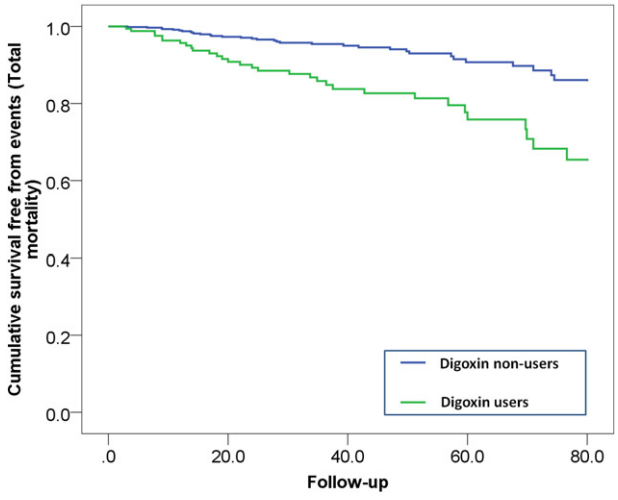

Fig. 1. Kaplan–Meier curve estimates of survival free from total mortality according to the use of digoxin (green line) or not (blue line).

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.