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Predictors of digoxin use and risk of mortality in ED patients with atrial fibrillation: Results from the Chinese AF registry

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ABSTRACT

Objectives: The aim of this study was to evaluate factors of digoxin use and its relation to mortality in ED patients with atrial fibrillation (AF).

Methods: The Chinese AF registry enrolled 2016 AF patients from 20 representative EDs, and the period of study was one year. Predictors of digoxin use and its relation to mortality were assessed by logistic and Cox regression analyses.

Results: Digoxin was assigned in 609 patients (30.6%), and younger age, lower body mass index values, and existence of permanent AF, heart failure (HF), chronic obstructive pulmonary disease, and valvular heart disease were identified to be factors associated with digoxin use. During the follow-up, compared to patients without digoxin therapy, digoxin-treated patients had significantly higher risk of all-cause death (17.2% vs. 13.0%, $P = 0.012$) and cardiovascular death (15.1% vs. 6.7%, $P < 0.001$), but similar risk of sudden cardiac death (1.1% vs. 0.7%, $P = 0.341$). However, after adjustment for related covariates, digoxin use was no longer notably associated with increased all-cause mortality (hazards ratio [HR] 0.973, 95% confidence interval [CI] 0.718–1.318) and cardiovascular death (HR 1.313, 95% CI 0.905–1.906). Besides, neutral associations of digoxin treatment to mortality were obtained in relevant subgroups, with no interactions observed between digoxin and gender, HF, valvular heart disease, or concomitant warfarin treatment in mortality risk.

Conclusions: In ED patients with AF, digoxin was more frequently assigned to vulnerable patients with concomitant HF or valvular heart disease, and digoxin use was not related to a significantly increased risk of mortality.

1. Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac rhythm disturbance encountered in clinical practice, and affects >30 million individuals worldwide [1]. AF significantly increases the risk of morbidity and mortality, causing great threat to public health and substantial medical expenses [2]. Apart from anticoagulant therapy for the prevention of thromboembolic complications in high-risk patients, maintaining sinus rhythm or controlling ventricular rate is another vital aspect in the management of AF [3]. Digoxin, due to its effects of slowing down the conduction in the AV node and increasing the refractory period, has been widely applied in patients with AF to achieve rate control, alone or in combination with β blockers or non-dihydropyridine calcium channel antagonists.

Although digoxin has been endorsed as a class I recommendation in the current guidelines for rate control in AF patients concomitant heart failure (HF) and left ventricular dysfunction [3], the effect of digoxin use on mortality remains controversial. The Digitalis Investigation Group (DIG) study, as the landmark randomized controlled trial (RCT) designed to evaluate the effect of digoxin on mortality among patients with HF, indicated a neutral relation of digoxin use and all-cause mortality [4]. However, a definite relation of digoxin use on mortality in the setting of AF has not been elucidated, as post-hoc analyses of observational studies and RCTs with distinct research designs and purposes revealing contradictory associations between digoxin use and survival

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[5-22]. Besides, factors related to digoxin use and its relation to mortality has been rarely examined in real-world AF patients attending emergency departments (EDs), thus we aimed to explore these issues in this study by conducting an analysis of a prospective multicenter AF registry in China.

2. Methods

2.1. Study design and participants

The Chinese AF registry was a multicenter prospective study and aimed to evaluate the clinical characteristics, treatments, and 1-year outcomes of ED patients presenting with a diagnosis of AF from November 2008 to October 2011. A total of 20 centers representing different levels of medical care in China (i.e., academic and non-academic, urban and rural, general and specialized) were selected to participate in the AF registry, and all centers were encouraged to recruit patients consecutively. Patients of interest were identified by reviewing clinical records and electronic databases. The diagnosis of AF was verified by research staff by screening their electrocardiograms, records of Holter monitor and rhythm strip according to clinical guidelines of AF [3]. Treatment decisions were made at the discretion of the treating physician. Study protocols were approved by the ethics committee of each center and complied with the principles outlined in the Declaration of Helsinki. All participants were provided with written informed consent.

2.2. Data collection and processing

Patients' demographic information, admission vital signs, medical histories, and treatments were collected at baseline by interviewing the participants, reviewing their medical records, and contacting their treating physicians. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Patients were classified according to their type of AF: paroxysmal AF, persistent AF, and permanent AF based on recommendations of clinical guidelines [3]. Blood pressure (BP) was accurately measured at least twice and the average were recorded by treating physicians via mercury sphygmomanometers according to the American Heart Association's scientific statement on human BP determination by sphygmomanometer [23]. Heart rate was measured by 12-lead electrocardiography in the supine position after at least 3 min of rest. Medical histories, including myocardial infarction (MI), coronary artery disease (CAD), congenital heart disease, valvular heart disease, heart failure (HF), hypertension, diabetes mellitus (DM), previous stroke or transient ischemic attack (TIA), chronic obstructive pulmonary disease (COPD), dementia, hyperthyroidism, previous major bleeding, and smoking, were also collected at baseline. The diagnosis of HF was made according to clinical guidelines of HF [24]. Left ventricular ejection fraction (LVEF) was measured using Simpson's biplane method [25]. The $CHADS_2$ score was calculated by assigning 1 point each for the presence of congestive HF, hypertension, age ≥ 75 years, DM, and 2 points for previous stroke/TIA [3]. Besides, medical therapies, including aspirin, warfarin, clopidogrel, statin, β blockers, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), diuretic, calcium channel blocker, and anti-arrhythmia agents were obtained from medical records and electronic databases.

2.3. Follow-up and outcome definition

Follow-up was completed in November 2012 by trained research personnel via clinic visit, telephone or delivery of medical records, with a mean follow-up period of 1 year. In the present study, primary outcome was all-cause mortality, and secondary outcomes were defined as cardiovascular death and sudden cardiac death, as assessed by an independent outcome adjudication committee through reviewing all the events in a blinded, preplanned fashion. Cardiovascular death included sudden cardiac death, and death caused by heart failure, stroke, myocardial infarction, pulmonary embolus, peripheral embolus, aortic dissection, etc. Sudden cardiac death was defined as natural death from various types of cardiac causes, with an abrupt attack and rapid progress to death within 1 h of the onset of acute symptoms.

2.4. Statistical analysis

Continuous variables were expressed as means with standard deviations or medians with quartiles; categorical variables were expressed as frequencies and percentages. Differences in continuous variables between patients grouped according to digoxin use were analyzed using unpaired *t*-test or the Mann-Whitney *U* test; comparison of categorical variables was performed using chi-$\chi 2$ test or Fisher's exact test.

Logistic regression analysis was utilized to identify factors related to digoxin receipt. Kaplan-Meier curves and log-rank tests were conducted to illustrate survival discrepancies between digoxin-treated and untreated patients. Cox proportional hazards models were performed to evaluate the effects of digoxin therapy on the incidence of all-cause mortality, cardiovascular death, and sudden cardiac death, with additional covariates (including age, sex, BMI, admission vital signs, type of AF, medical histories, and concomitant treatments) included into multivariable Cox models to assess the independent association of digoxin use to the defined outcomes. Besides, we performed subgroup analyses to evaluate whether discrepancies in the association of digoxin use and mortality existed among the following specific subsets of patients, including sex, presence of HF and valvular heart disease, and concomitant use of warfarin. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in comparison with no digoxin use.

The software package SPSS version 22.0 (IBM Corporation, New York, NY, USA) was used for statistical analysis. All statistical tests were 2-tailed, and a P value <0.05 were considered significant.

3. Results

Of the 2016 patients with AF, 25 patients were excluded due to incomplete data, and 1991 patients with a mean age of 68.5 years and 1093 females (54.9%) were included in the present study. Of the 1991 patients, 609 patients (30.6%) were treated with digoxin.

Baseline characteristics and treatments are shown in Table 1. Compared to patients without digoxin therapy, those treated with digoxin were significantly younger, more likely to be female, and had lower BMI and systolic blood pressure values; they tended to present with AF as a secondary diagnosis, and suffered from non-paroxysmal AF, congenital heart disease, valvular heart disease, HF, COPD, and smoking more frequently, while less likely to coexist with CAD, hypertension, previous stroke or TIA, and hyperthyroidism. Besides, no remarkable difference existed in the prevalence of MI, DM, dementia, previous major bleeding and $CHADS_2$ scores between these two groups. For treatment, patients in digoxin group received warfarin, aspirin, β blocker, ACEI, and diuretic more frequently, while less likely to take clopidogrel, statin, dihydropyridine and anti-arrhythmia agents. In addition, significantly higher proportion of digoxin prescription was observed in patients recruited from rural areas (49.5%) compared to patients recruited in the urban setting (24.3%), and this practice was in accordance with much higher prevalence of HF and left ventricular systolic dysfunction in rural patients than urban patients (Supplementary table 1).

The factors related to digoxin use are shown in Table 2. In the multivariable logistic regression models, younger age, lower BMI values, and existence of non-paroxysmal AF, HF, LVEF <45%, COPD, and valvular heart disease were identified to be predictors associated with digoxin treatment, and existence of permanent AF, HF, and valvular heart disease were indicated to be strong predictors of digoxin use in patients recruited both from rural areas and urban areas (Supplementary table 2). Outcomes and associations between digoxin use and risk of mortality

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