

Digoxin is associated with worse outcomes in patients with heart failure with reduced ejection fraction

Jingmin Zhou^{1†}, Juan Cao^{1,2†}, Xuejuan Jin¹, Jun Zhou¹, Zhenyue Chen³, Dingli Xu⁴, Xinchun Yang⁵, Wei Dong⁶, Liwen Li⁷, Yuyuan Fan^{2,1}, Li Chen², Qiaoqing Zhong⁸, Micheal Fu⁹, Kai Hu¹, Junbo Ge^{1*} on behalf of CN-HF investigators

¹Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, 180 Fenglin Road, Shanghai 200032, China; ²North Sichuan Medical College, Department of Cardiology, The Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China; ³Department of Cardiology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; ⁴Department of Cardiology, Nanfang Hospital, Southern Medical University, Guangzhou, China; ⁵Heart Center, Beijing Chaoyang Hospital affiliated to Capital Medical University, Beijing, China; ⁶Department of Cardiology, Chinese People's Liberation Army General Hospital, Beijing, China; ⁷Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; ⁸Department of Cardiology, First People's Hospital of Chenzhou, Chenzhou, China; ⁹Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital/Östra Hospital, University of Gothenburg, Gothenburg, Sweden

Abstract

Aims The aim of this study was to investigate the impact of digoxin use on the outcomes of patients with heart failure with reduced ejection fraction (HFrEF) and its possible interaction with atrial fibrillation or use of currently guideline-recommended treatments in the real world in China.

Methods and results Patients hospitalized with HFrEF from 45 hospitals participating in the China National Heart Failure Registration Study (CN-HF) were enrolled to assess the all-cause mortality, HF mortality, all-cause re-hospitalization, and HF re-hospitalization associated with digoxin use. Eight hundred eighty-two eligible HFrEF patients in the CN-HF registry were included: 372 patients with digoxin and 510 patients without digoxin. Among them, 794 (90.0%) patients were followed up for the endpoint events, with a median follow-up of 28.6 months. Kaplan–Meier survival analysis showed that the all-cause mortality ($P < 0.001$) and all-cause re-hospitalization ($P = 0.020$) were significantly higher in digoxin group than non-digoxin group, while HF mortality ($P = 0.232$) and HF re-hospitalization ($P = 0.098$) were similar between the two groups. The adjusted Cox proportional-hazards regression analysis demonstrated that digoxin use remained as an independent risk factor for increased all-cause mortality [hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.27–2.44; $P = 0.001$] and all-cause re-hospitalization (HR 1.27; 95% CI 1.03–1.57; $P = 0.029$) in HFrEF patients and the predictive value of digoxin for all-cause mortality irrespective of rhythm or in combination with other guideline-recommended therapies.

Conclusions Digoxin use is independently associated with increased risk of all-cause mortality and all-cause re-hospitalization in HFrEF patients.

Keywords Digoxin; Heart failure; Atrial fibrillation; Prognosis

Received: 12 June 2019; Revised: 2 September 2019; Accepted: 17 September 2019

*Correspondence to: Junbo Ge, Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, 180 Fenglin Road, Shanghai 200032, China. Tel.: +86 21 6404 1990 ext 2745; Fax: +86 21 6443 7078.

Email: jbge@zs-hospital.sh.cn

†These authors contributed equally to this work.

Clinical Trial Registration: <http://www.clinicaltrials.gov/ct2/home> (ID: NCT02079428).

Introduction

Digoxin is recommended in patients with heart failure with reduced ejection fraction (HFrEF) who continue to be symptomatic despite optimal therapy including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers

(ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and diuretics as needed for fluid control or rate control in the presence of atrial fibrillation (AF).^{1,2} Available randomized clinical trials have shown that digoxin improved clinical symptoms and lowered rates of hospitalization for HF but did not improve survival.^{3–8} It is of note that almost all

these trials were performed prior to conventional use of modern HF therapies including beta-blockers, MRAs, and device therapies (e.g. implantable cardioverter–defibrillators and cardiac resynchronization therapy); thus, cautions are needed to translate previous study results of digoxin into today's clinical practice. In the meantime, recent studies based on either registry database or retrospective analysis showed that digoxin use was associated with increased risk of all-cause mortality in HFrEF patients.^{9–13} As the use of digoxin varied according to country and ethnicity,^{14–19} in particular in China where the majority of HFrEF patients were treated with digoxin, and some traditional Chinese medicines (TCMs), for example, qili qiangxin capsules, had been shown effective in surrogate endpoints and thus have been recommended by current Chinese guideline for HF, which might interfere with digoxin use.^{1,20,21} Therefore, there are great concern about both efficacy and safety of digoxin in the context of contemporary management of HFrEF in China.

Data of this study were derived from the China National Heart Failure Registration Study (CN-HF). The present study aimed to analyse the impact of digoxin use on the outcomes of patients with HFrEF and its possible interaction with AF or use of currently guideline-recommended treatments (ACEIs/ARBs, beta-blockers, MRAs) in China.

Methods

Study population

The CN-HF (ID: NCT02079428) was a nationwide, multicentre, prospective registry study that included patients with HF from 45 participating centres across nine regions in China between January 2013 and December 2015. Diagnostic criteria of HF were based on 2014 Chinese guidelines for the diagnosis and treatment of chronic HF.¹ The patients were followed up for 6, 12, 24, and 36 months after discharge, and the registrations were managed through online electronic system. Informed consent was obtained from all patients.

In this study, patients were eligible if left ventricular ejection fraction (LVEF) was 40% or less. Patients with significant renal dysfunction (creatinine > 3.0 mg/dL), potassium < 3.2 mmol/L or potassium > 5.5 mmol/L, or withdrawal after short-term oral digoxin treatment (≤30 days) were excluded.

The study conformed to the Declaration of Helsinki and was approved by all participating hospital ethics committees.

Data collection

Data regarding demographic information, physical examination, laboratory index, echocardiography, co-morbidities, medications, and clinical outcomes were obtained from

CN-HF. Patients were divided into two groups on the basis of the use of digoxin: non-digoxin group and digoxin group. The primary endpoint of this study was all-cause mortality; the secondary endpoints were HF mortality, all-cause re-hospitalization, and HF re-hospitalization.

Statistical analyses

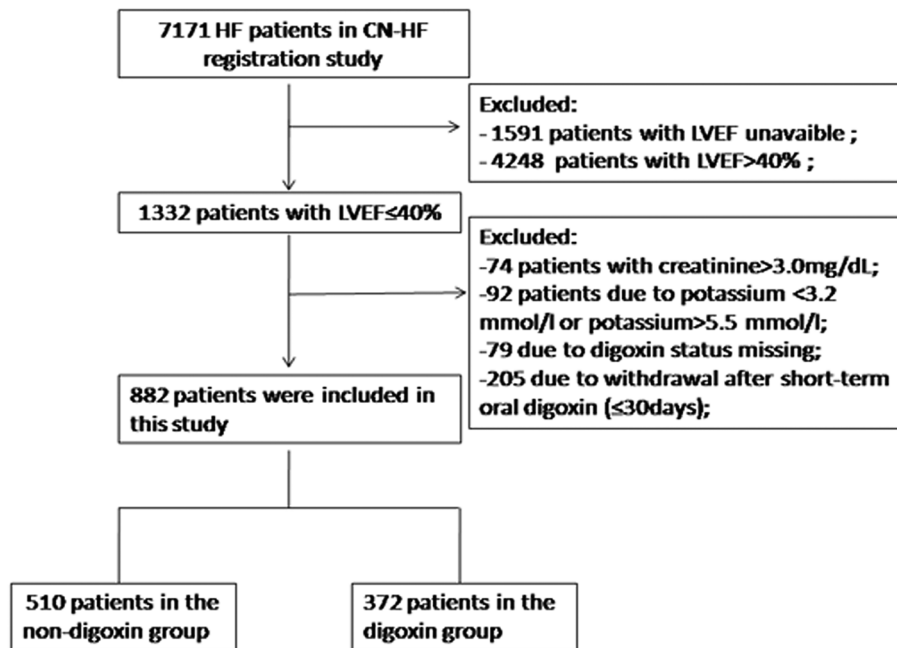
Continuous variables were presented as mean values with standard deviations (mean ± SD) or median (interquartile range), whereas categorical variables were displayed as counts and percentages. Differences between the two groups were compared using Student's *t*-test or Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Kaplan–Meier curves and log-rank test were used to describe and compare time to events. Cox proportional-hazards regression models were used to examine the independent association of digoxin use and the risk of adverse outcomes, and the following covariates were included in the model: age, systolic blood pressure (SBP), LVEF, New York Heart Association (NYHA) class, sodium, potassium, creatinine, haemoglobin, AF, and the use of digoxin, ACEIs/ARBs, beta-blockers, and MRAs. Additional models were performed by concurrent use of other drugs (ACEIs/ARBs, beta-blockers, and MRAs), with or without AF.

All *P*-values reported were two-sided, and *P* < 0.05 was considered statistically significant. Statistical calculations were performed using SPSS software version 23.0.

Results

Study population

A total of 7171 patients were registered in CN-HF: 5580 patients with LVEF available and 1332 defined as HFrEF. Among HFrEF patients, 74 were excluded owing to renal dysfunction, 92 due to potassium < 3.2 mmol/L or potassium > 5.5 mmol/L, 79 due to unknown digoxin medication status, and 205 due to withdrawal after short-term oral digoxin (≤30 days). Finally, 882 patients were included in this study, with 372 (42.2%) patients in the digoxin group and 510 (57.8%) patients in the non-digoxin group (*Figure 1*). Among the 232 (26.3%) patients with AF, the use of ACEIs/ARBs, beta-blockers, and MRAs was as high as 79.9%, 70.3%, and 89.0%, respectively. Regarding digoxin dose, 6.7%, 0.3%, 89.5%, and 1.3% of patients were treated with 0.25, 0.125–0.25, 0.125, and 0.0625 mg/day, respectively, whereas for the rest of 2.2% of patients, the dose of digoxin was unknown.

Figure 1 Flowchart of the study population. LVEF, left ventricular ejection fraction.

Baseline characteristics

Patients who received digoxin were younger and had lower LVEF, less co-morbidities of hypertension and myocardial infarction, and less statins and aspirin use but had higher heart rate, higher NYHA class and haemoglobin level, higher co-morbidity of AF, and more MRAs use (*Table 1*).

Outcome analysis

A total of 794 (90.0%) patients completed follow-up; the median follow-up duration was 28.6 months (interquartile range 13.1–40.2 months); death occurred in 162 (18.4%) patients, with 67 deaths due to HF; 374 (42.4%) patients were re-hospitalized, with 235 re-hospitalizations due to HF.

Kaplan–Meier survival curves and log-rank test showed that the cumulative risk of all-cause mortality ($P < 0.001$) and all-cause re-hospitalization ($P = 0.020$) was significantly higher in the digoxin group than in the non-digoxin group (*Figures 2 and 3*), while the cumulative risk of HF mortality ($P = 0.232$) and HF re-hospitalization ($P = 0.098$) was similar between the two groups.

Cox proportional-hazards regression analysis demonstrated that digoxin use was associated with higher risk of all-cause mortality [hazard ratio (HR) 1.76; 95% CI 1.27–2.44; $P = 0.001$] and all-cause re-hospitalization (HR 1.27; 95% CI 1.03–1.57; $P = 0.029$) after adjustment for baseline age, SBP, LVEF, NYHA class, sodium, potassium, creatinine,

haemoglobin, AF, and the use of ACEIs/ARBs, beta-blockers and MRAs (*Table 2*).

Interaction of digoxin use on outcomes in atrial fibrillation vs. non-atrial fibrillation

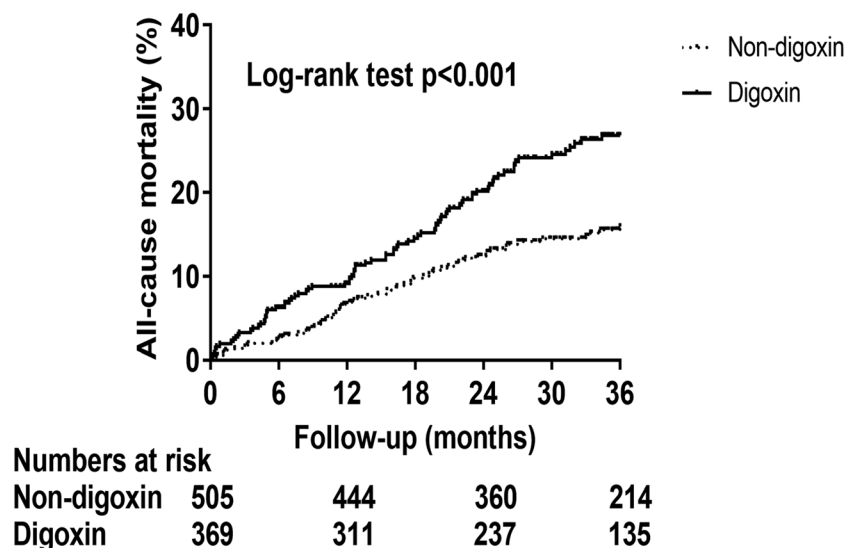
There were 232 patients (26.3%) with AF. The HF_{rEF} patients were categorized into following four subgroups: 399 patients (45.2%) without AF and did not receive digoxin (Digoxin–AF–), 251 patients (28.5%) without AF but received digoxin (Digoxin+AF–), 111 patients (12.6%) with AF but did not receive digoxin (Digoxin–AF+), and 121 patients (13.7%) with AF and received digoxin (Digoxin+AF+). Rates of all-cause mortality of Digoxin–AF–, Digoxin+AF–, Digoxin–AF+, and Digoxin+AF+ were 13.0%, 19.9%, 18.9%, and 32.2%, respectively; rates of HF mortality of Digoxin–AF–, Digoxin+AF–, Digoxin–AF+, and Digoxin+AF+ were 6.5%, 8.8%, 8.1%, and 8.3%, respectively; rates of all-cause re-hospitalization of Digoxin–AF–, Digoxin+AF–, Digoxin–AF+, and Digoxin+AF+ were 38.3%, 46.2%, 37.8%, and 52.1%, respectively; rates of HF re-hospitalization of Digoxin–AF–, Digoxin+AF–, Digoxin–AF+, and Digoxin+AF+ were 25.1%, 31.1%, 21.6%, and 27.3%, respectively.

As shown in *Table 3*, compared with the reference group (Digoxin+AF+), all-cause mortality was lower in both the Digoxin–AF+ group (HR 0.48; 95% CI 0.28–0.83; $P = 0.009$) and Digoxin–AF– group (HR 0.42; 95% CI 0.27–0.65; $P < 0.001$), and all-cause re-hospitalization risk was lower in the Digoxin–AF+ group (HR 0.64; 95% CI 0.43–0.95; $P =$

Table 1 Baseline characteristics of the study population

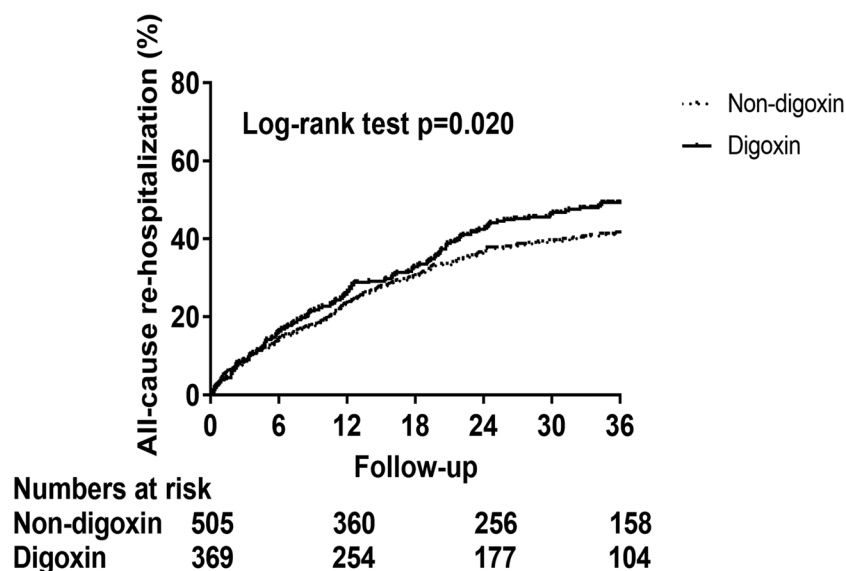
Characteristics	All (n = 882)	Non-digoxin (n = 510)	Digoxin (n = 372)	P value
Age (years)	64.9 ± 14.2	66.1 ± 13.7	63.3 ± 14.8	0.004
Female	233 (26.4%)	125 (24.5%)	108 (29.0%)	0.132
Heart rate (bpm)	85.7 ± 19.4	83.2 ± 18.6	89.1 ± 20.0	<0.001
SBP (mmHg)	126.3 ± 21.3	127.3 ± 21.2	125.0 ± 21.4	0.121
NYHA class				<0.001
I	20 (2.3%)	17 (3.3%)	3 (0.8%)	
II	197 (22.3%)	142 (27.8%)	55 (14.8%)	
III	459 (52.0%)	238 (46.7%)	221 (59.4%)	
IV	206 (23.4%)	113 (22.2%)	93 (25.0%)	
LVEF (%)	31.9 ± 6.6	32.7 ± 6.4	30.7 ± 6.7	<0.001
Na (mmol/L)	139.8 ± 6.0	140.1 ± 4.0	139.3 ± 8.0	0.059
K (mmol/L)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.554
Cr (umol/L)	1.1 (0.8,1.3)	1.0 (0.9,1.3)	1.0 (0.8,1.3)	0.137
Hb (g/L)	131.3 ± 19.7	129.6 ± 19.4	133.7 ± 19.2	0.002
Co-morbidities				
Hypertension	451 (51.1%)	279 (54.7%)	172 (46.2%)	0.013
Myocardial infarction	188 (21.3%)	133 (26.1%)	55 (14.8%)	<0.001
Hyperlipidaemia	80 (9.1%)	49 (9.6%)	31 (8.3%)	0.515
Diabetes mellitus	217 (24.6%)	126 (24.7%)	91 (24.5%)	0.934
AF	232 (26.3%)	111 (21.8%)	121 (32.5%)	<0.001
Medications				
ACEIs/ARBs	705 (79.9%)	409 (80.2%)	296 (79.6%)	0.819
Beta-blockers	620 (70.3%)	362 (71.0%)	258 (69.4%)	0.602
MRAs	785 (89.0%)	429 (84.1%)	356 (95.7%)	<0.001
Nitrates	429 (48.6%)	245 (48.0%)	184 (49.5%)	0.676
Statins	403 (45.7%)	251 (49.2%)	152 (40.9%)	0.014
Aspirin	462 (52.4%)	287 (56.3%)	175 (47.0%)	0.007
TCM	159 (18.0)	84 (16.5%)	75 (20.2%)	0.159

ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; Cr, Creatinine; Hb, Haemoglobin; K, serum potassium; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; Na, serum sodium; NYHA, New York Heart Association; SBP, systolic blood pressure; TCM, traditional Chinese medicine.

Figure 2 Kaplan–Meier cumulative risk of all-cause mortality in patients with and without digoxin.

0.028) (Table 3). And the Digoxin+AF– group had a 61% increase in all-cause mortality risk when the Digoxin–AF– group served as a reference group (HR 1.61; 95% CI

1.08–2.40; $P = 0.021$). In short, digoxin is an independent predictor of all-cause mortality in HFref patients, with both AF and non-AF.

Figure 3 Kaplan–Meier cumulative risk of all-cause re-hospitalization in patients with and without digoxin.**Table 2** Multivariate Cox proportional-hazards models for predictions of time to different endpoint events by use of digoxin

Outcomes	Events <i>n</i> (%)		HR	95% CI	<i>P</i> value
	Non-digoxin	Digoxin			
All-cause mortality	73 (14.3%)	89 (23.9%)	1.76	1.27–2.44	0.001
HF mortality	35 (6.9%)	32 (8.6%)	1.31	0.79–2.16	0.296
All-cause re-hospitalization	195 (38.2%)	179 (48.1%)	1.27	1.03–1.57	0.029
HF re-hospitalization	124 (24.3%)	111 (29.8%)	1.19	0.91–1.55	0.213

Multivariate Cox regression model adjustment for baseline age, SBP, LVEF, NYHA class, sodium, potassium, creatinine, haemoglobin, atrial fibrillation (AF) and the use of ACEIs/ARBs, beta-blockers and MRAs.
CI, confidence interval; HR, hazard ratio.

Table 3 Hazard ratios and 95% CI of digoxin associated with cardiac endpoints for the subgroups

	All-cause mortality	HF mortality	All-cause re-hospitalization	HF re-hospitalization
Digoxin–AF–	0.42 (0.27–0.65)*	0.88 (0.41–1.89)	0.83 (0.61–1.13)	1.07 (0.71–1.60)
Digoxin+AF–	0.68 (0.44–1.05)	1.20 (0.55–2.64)	0.98 (0.71–1.34)	1.23 (0.81–1.86)
Digoxin–AF+	0.48 (0.28–0.83)*	0.86 (0.34–2.21)	0.64 (0.43–0.95)*	0.77 (0.45–1.31)
Digoxin+AF+	1	1	1	1

Multivariate Cox regression model adjustment for age, SBP, LVEF, NYHA class, sodium, potassium, creatinine, haemoglobin, and the use of ACEIs/ARBs, beta-blockers and MRAs.

CI, confidence interval.

* $P < 0.05$.

Impact of digoxin use on outcome in uses of other drugs

Six hundred twenty (70.3%) patients received beta-blockers. There were 258 patients in digoxin group and 362 patients in non-digoxin group; the rates of all-cause mortality, HF mortality, all-cause re-hospitalization, and HF re-hospitalization were 16.1%, 7.4%, 41.5%, and 27.6%, respectively; and

digoxin was significantly associated with a 90% increase in all-cause mortality risk (HR 1.90; 95% CI 1.24–2.91; $P = 0.003$) (Table 4).

A total of 705 patients (79.9%) were treated with ACEIs/ARBs. Among the 296 patients in the digoxin group and 409 patients in the non-digoxin group, death occurred in 107 (15.2%) patients, 48 (6.8%) patient deaths were due to HF; 283 (40.1%) patients were re-hospitalized, and 187

Table 4 Hazard ratios and 95% CI for different endpoint events of drugs (digoxin vs. non-digoxin users)

	Non-digoxin	Digoxin	HR	95% CI	P value
Beta-blockers					
All-cause mortality	41 (11.3%)	59 (22.9%)	1.90	1.24–2.91	0.003
HF mortality	23 (6.4%)	23 (8.9%)	1.30	0.70–2.43	0.410
All-cause re-hospitalization	135 (37.3%)	122 (47.3%)	1.16	0.89–1.51	0.274
HF re-hospitalization	92 (25.4%)	79 (30.6%)	1.07	0.78–1.48	0.674
ACEIs/ARBs					
All-cause mortality	50 (12.2%)	57 (19.3%)	1.48	0.98–2.22	0.061
HF mortality	24 (5.9%)	24 (8.1%)	1.35	0.74–2.47	0.333
All-cause re-hospitalization	149 (36.4%)	134 (45.3%)	1.26	0.99–1.62	0.066
HF re-hospitalization	99 (24.2%)	88 (29.7%)	1.23	0.90–1.66	0.190
MRAs					
All-cause mortality	62 (14.5%)	82 (23.0%)	1.68	1.20–2.37	0.003
HF mortality	33 (7.7%)	31 (8.7%)	1.28	0.77–2.13	0.346
All-cause re-hospitalization	171 (39.9%)	170 (47.8%)	1.23	0.99–1.54	0.061
HF re-hospitalization	115 (26.8%)	108 (30.3%)	1.17	0.89–1.54	0.254
ACEIs/ARBs, beta-blockers, and MRAs					
All-cause mortality	29 (10.9%)	41 (19.9%)	1.70	1.01–2.86	0.047
HF mortality	18 (6.8%)	17 (8.3%)	1.19	0.57–2.51	0.643
All-cause re-hospitalization	100 (37.7%)	92 (44.7%)	1.16	0.85–1.57	0.356
HF re-hospitalization	72 (27.2%)	62 (30.1%)	1.12	0.78–1.62	0.544

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; MRAs, mineralocorticoid receptor antagonists.

(26.5%) re-hospitalization was due to HF. The use of digoxin was associated with the increased trend of all-cause mortality risk (HR 1.48; 95% CI 0.98–2.22; $P = 0.061$) (Table 4).

Among those on treatment with MRAs ($n = 785$), 356 patients were in the digoxin group and 429 patients in the non-digoxin group. The all-cause mortality (HR 1.68; 95% CI 1.20–2.37; $P = 0.003$) was higher in the digoxin group compared with non-digoxin group (Table 4).

In those treated with ACEIs/ARBs, beta-blockers, and MRAs ($n = 471$), 206 patients were in the digoxin group and 265 patients in the non-digoxin group. Digoxin increased the risk of all-cause mortality by 70% compared with that in the non-digoxin group (HR 1.70; 95% CI 1.01–2.86; $P = 0.047$) (Table 4).

Discussion

On the basis of data derived from this nationwide registry study of HFrEF in China, we found that use of digoxin is associated with a higher risk of all-cause mortality in HFrEF patients, irrespective of heart rhythm and use of other guideline-recommended therapy.

Efficacy of digoxin in patients with HF has been studied previously in Western countries. In Digitalis Investigation Group (DIG), trial digoxin was not associated with increased risk of overall mortality; in fact, digoxin use was related to reduced risk of all-cause re-hospitalization and HF re-hospitalization in patients with HF of LVEF $\leq 45\%$.⁸ In the subgroup analysis of the DIG trial (NYHA Class III–IV symptoms, LVEF $< 25\%$, or cardiothoracic ratio $> 55\%$), digoxin significantly improved the outcomes of clinically important

combined endpoints of mortality or hospitalizations in chronic HF patients.²² Our analysis, however, suggested that digoxin use is associated with increased all-cause mortality and all-cause re-hospitalization in HFrEF patients. Our finding is similar to that of a nationwide propensity score-matched study in Denmark, which also showed that digoxin use was linked with an increased risk of all-cause mortality in HF patients.⁹ Similar results were also demonstrated in other studies.^{10–12}

One important question is why efficacy and safety from DIG trial could not be reproduced in recent studies in real-world settings. Several issues are worthy to be discussed. Firstly, the background therapy of DIG trial did not represent the contemporary guideline-directed medical therapy (GDMT). As a matter of fact, data were not available regarding the use of beta-blockers and MRAs in DIG trial. It is well known that beta-blockers and MRAs could improve survival of HFrEF patients. Secondly, there was selection bias in the DIG trial in which around 40% of the study population were treated with digoxin prior to the study. This might ensure the tolerability in favour for digoxin. However, this is not the case in a real-world scenario as in the case of this registry study. According to current guideline, digoxin could be initiated in patients who remain symptomatic despite recommended treatment with ACEIs/ARBs, beta-blockers, MRAs, and diuretics when necessary. Thirdly, as is the nature of a randomized controlled trial such as the DIG trial, patients were monitored closely by a special study team, whereas this is not the case in the real world. Ideally, regular monitoring might increase the safety of digoxin use owing to the narrow therapeutic dose range of digoxin.

Another important question is why digoxin use is associated with increased all-cause mortality in current study.

Several possibilities exist. Patients in digoxin group in the present study were probably sicker than non-digoxin group, as former patients had higher heart rate, higher prevalence of NYHA III–IV, lower EF, and more MRAs; all these factors might indicate that these patients may carry higher risk for mortality. Indeed, by applying the multivariable Cox regression, we tried to adjust the variables as much as we could. Moreover, the therapeutic effect and toxic effect of digoxin were known to be closely related to the serum digoxin concentration owing to its narrow therapeutic index. The Propensity Matched Study of the DIG trial suggested that digoxin at low serum digoxin concentration significantly reduced mortality and hospitalizations in HF patients.²³ In fact, up to 90.8% of patients in our cohort took digoxin at a dose of no more than 0.125 mg/day. However, we cannot exclude the possibility that Chinese patients with HF might tolerate less to digoxin than in Western countries owing to ethnicity.

In addition, the reasons for digoxin intake increased all-cause mortality, and all-cause re-hospitalization but not HF mortality and HF re-hospitalization is also worth exploring. One of the possible explanations is that patients with digoxin are more seriously ill and are more often have other accompanying non-cardiovascular co-morbidities. All these together make these patients prone to have increased all-cause mortality and all-cause re-hospitalization. Regarding serum digoxin concentrations, unfortunately, we did not have such data, as serum digoxin concentration was not measured routinely in daily clinical practice if there was no clinical suspect of digoxin toxicity.

Our findings extended previous studies in four aspects. Firstly, compared with the Danish registry study, CN-HF reported more contemporary HF management.⁹ In the Danish registry study, rate of ACEIs/ARBs use was 54%, beta-blockers was 39.5%, and MRAs was 20.0%, whereas in CN-HF, rate of ACEIs/ARBs use was 79.9%, beta-blockers was 70.3%, and MRAs was 89.0%. This difference not only reflects geographic heterogeneity in HF management but also makes our study more relevant at least for the Chinese HF population. Secondly, our study confirmed results from the Danish study indicating that digoxin is associated with increased all-cause mortality in a real-world setting regardless of geographic difference. This is particularly relevant as in China some TCMs were recommended to treat HF.²⁰ Thirdly, in our study, we were able to make a comprehensive assessment of possible impact of digoxin by concurrent use of temporary GDMT. This is a highly relevant issue for HFrEF population, as digoxin is administered after optimal use of GDMT, which was not studied in the DIG trial. We evaluated possible interactions of impact of digoxin by AF. Despite that AF is one of the most common arrhythmias in HF patients and digoxin is often used to control the heart rate in patients with HFrEF and concomitant AF, the impact of digoxin on the prognosis of these patients is still controversial.^{24,25} Our findings were in line with recent study that showed digoxin increasing mortality in AF patients with HF.²⁶

There are some limitations in this study. Firstly, this study refers a small patient cohort because LVEF \leq 40% was found only in a small population in CN-HF register. A similar finding was reported in other Asian HF registries.^{27–29} Secondly, our research data are derived from 45 different hospitals, which are highly heterogeneous. For example, although we have conducted strict, unified, and standardized training for participants in different hospitals, the specific treatment plan of patients depends on different clinicians. There are also significant difficulties in controlling confounding factors, although the multivariable Cox regression analysis is used to control confounding factors as much as possible, and we cannot control factors that are not included and may influence the results of this study. In other words, the conclusions were established on the premise that the existing confounding factors involved in this study were adjusted, so they still need to be further confirmed by randomized clinical trials. Thirdly, there are many kinds of TCMs; some of them are served as soups whereas others as capsule, depending on the characteristics of the patient. Generally, qili qiangxin capsule is one of the most common prescribed TCMs in HF. The TCMs in each of the 45 hospitals are different. We can only know from our research database whether these patients received TCMs but did not obtain the information about specific drug kind and usage. This article reflects the current status of treatment in patients with HF in China. To date, there are at least three types of TCMs that are believed to affect the metabolism of digoxin including: (i) ginseng-containing preparations, which can directly excite myocardium and strengthen heart function, thus enhance each other when combined with digoxin, which is prone to digoxin toxicity; (ii) licorice-enriched preparation that might reduce the K⁺ in the body and thus make the heart more sensitive to digoxin; and (iii) calcium-containing preparation, which can enhance the effect of digoxin and thus increase the toxicity, causes arrhythmia and conduction block.³⁰ Finally, serum digoxin concentrations were not monitored and analysed. However, the strength of this study is data from a prospective HF registry in China where both population and care modality in HF may differ from Western countries.

Conclusions

In this nationwide registry study of HFrEF, we found that use of digoxin was an independent predictor of all-cause mortality in HFrEF patients, irrespective of contemporary guideline-recommended therapy and in patients with AF and non-AF.

Acknowledgements

We would like to acknowledge all the investigators in the following research sites for making data available for public use.

- (1) Qiaoqing Zhong. Chenzhou No. 1 People's Hospital, Chenzhou, China
- (2) Yingmin Lu. Xin Hua Hospital affiliated to Shanghai Jiao Tong University School of Medicine Chongming branch, Shanghai, China
- (3) Guohui Zhang. Zhenjiang First People's Hospital, Zhenjiang, China
- (4) Li Chen. Affiliated Hospital of North Sichuan Medical College, Nanchong, China
- (5) Huimin Gu. First People's Hospital of Kunshan, Kunshan, China
- (6) Meng Wei. Shanghai Sixth People's Hospital, Shanghai, China
- (7) Lianglong Chen. Fujian Medical University Union Hospital, Fuzhou, China
- (8) Jun Wang. Jing'an District Central Hospital of Shanghai, Shanghai, China
- (9) Zhenyu Yang. Wuxi People's Hospital, Wuxi, China
- (10) Huigen Jin. Putuo People's Hospital of Shanghai, Shanghai, China
- (11) Xianliang Li. Zhangjiagang Hospital of Traditional Chinese Medicine, Zhangjiagang, China
- (12) Zengyong Qiao. Shanghai Fengxian District Central Hospital, Shanghai, China
- (13) Yingjun Yang. Jiashan First People's Hospital, Jiashan, China
- (14) Yulan Zhao. The Second Affiliated Hospital of Zhenzhou University, Zhengzhou, China
- (15) Ru Jia. The No.4 Hospital 1946 Jinan Shandong, Ji'nan, China
- (16) Bin Hong. Shanghai Qingpu District Central Hospital, Shanghai, China
- (17) Fang Yuan. Shanghai Chest Hospital, Shanghai, China
- (18) Jufei Wang. Fenghua Hospital, Fenghua, China
- (19) Jin Ma. Yangpu Hospital, Tongji University, Shanghai, China
- (20) Yu Xu. Henan Provincial People's Hospital, Zhengzhou, China
- (21) Liwen Li. Guangdong General Hospital, Guangzhou, China
- (22) Mahmud Wahafu. The Second People's Hospital of Kashgar Prefecture, Kashi, Xinjiang, China
- (23) Qin Yu. Zhongshan Hospital, Dalian University, Dalian, China
- (24) Changqian Wang. Shanghai Ninth People's Hospital, Shanghai, China
- (25) Changwu Ruan. Shanghai Eighth People's Hospital, Shanghai, China
- (26) Honggang Fu. Fuyuan People's Hospital, Qujing, China
- (27) Xuebo Liu. Shanghai East Hospital, Tongji University, Shanghai, China
- (28) Xin Xu. Wuxi No.2 People's Hospital, Wuxi, China
- (29) Shaoping Chen. Changhai Hospital of Shanghai, Shanghai, China
- (30) Qiliang Liu. Putuo District Center Hospital, Shanghai, China
- (31) Bei Shi. Hospital of Zunyi Medical College, Zunyi, China
- (32) Jiahong Xu. Tongji Hospital, Tongji University, Wuhan, China
- (33) Zhenyue Chen. Rui Jin Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China

Conflict of interest

None declared.

Funding

This study was supported by the National Science & Technology Pillar Program, 12th 5-year plan of China (2011BAI11B10).

References

1. Chinese guidelines for the diagnosis and treatment of heart failure 2014. *Zhonghua xin xue guan bing za zhi* 2014; **42**: 98–122.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
3. Lee DC, Johnson RA, Bingham JB, Leahy M, Dinsmore RE, Goroll AH, Newell JB, Strauss HW, Haber E. Heart failure in outpatients: a randomized trial of digoxin versus placebo. *N Engl J Med* 1982; **306**: 699–705.
4. Guyatt GH, Sullivan MJ, Fallen EL, Tihal H, Rideout E, Halcrow S, Nogradi S, Townsend M, Taylor DW. A controlled trial of digoxin in congestive heart failure. *Am J Cardiol* 1988; **61**: 371–375.
5. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989; **320**: 677–683.
6. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate

- chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol* 1993; **22**: 955–962.
7. Packer M, Gheorghide M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 1993; **329**: 1–7.
 8. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336**: 525–533.
 9. Madelaire C, Schou M, Nelveg-Kristensen KE, Schmiegelow M, Torp-Pedersen C, Gustafsson F, Kober L, Gislason G. Use of digoxin and risk of death or readmission for heart failure and sinus rhythm: a nationwide propensity score matched study. *Int J Cardiol* 2016; **221**: 944–950.
 10. Al-Khateeb M, Qureshi WT, Odeh R, Ahmed AM, Sakr S, Elshawi R, Bdeir MB, Al-Mallah MH. The impact of digoxin on mortality in patients with chronic systolic heart failure: a propensity-matched cohort study. *Int J Cardiol* 2017; **228**: 214–218.
 11. Freeman JV, Yang J, Sung SH, Hlatky MA, Go AS. Effectiveness and safety of digoxin among contemporary adults with incident systolic heart failure. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 525–533.
 12. Georgiopolou VV, Kalogeropoulos AP, Giamouzis G, Agha SA, Rashad MA, Waheed S, Laskar S, Smith AL, Butler J. Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. *Circ Heart Fail* 2009; **2**: 90–97.
 13. Konstantinou DM, Karvounis H, Giannakoulas G. Digoxin in heart failure with a reduced ejection fraction: a risk factor or a risk marker. *Cardiology* 2016; **134**: 311–319.
 14. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, Shirato K. Analysis of chronic heart failure registry in the Tohoku district: third year follow-up. *Circ J* 2004; **68**: 427–434.
 15. Patel N, Ju C, Macon C, Thadani U, Schulte PJ, Hernandez AF, Bhatt DL, Butler J, Yancy CW, Fonarow GC. Temporal trends of digoxin use in patients hospitalized with heart failure: analysis from the American Heart Association Get With The Guidelines-Heart Failure Registry. *JACC Heart Fail* 2016; **4**: 348–356.
 16. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan—first report from the CHART-2 study. *Circ J* 2011; **75**: 823–833.
 17. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozd J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2010; **12**: 1076–1084.
 18. Cao YM, Hu DY, Wang HY, Wu Y. A survey of medical therapies for chronic heart failure in primary hospitals in China. *Zhonghua Nei Ke Za Zhi* 2006; **45**: 907–909.
 19. Yu SB, Zhao QY, Cui HY, Qin M, Liu T, Kong B, Huang H, Huang CX. Investigation on the prevalence and related factors of medicinal therapy in patients with chronic systolic heart failure. *Zhonghua Liu Xing Bing Xue Za Zhi* 2012; **33**: 229–233.
 20. Chinese guidelines for the diagnosis and treatment of heart failure 2018. *Zhonghua Xin Xue Guan Bing Za Zhi* 2018; **46**: 760–789.
 21. Li X, Zhang J, Huang J, Ma A, Yang J, Li W, Wu Z, Yao C, Zhang Y, Yao W, Zhang B, Gao R. A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the effects of qili qiangxin capsules in patients with chronic heart failure. *J Am Coll Cardiol* 2013; **62**: 1065–1072.
 22. Gheorghide M, Patel K, Filippatos G, Anker SD, van Veldhuisen DJ, Cleland JG, Metra M, Aban IB, Greene SJ, Adams KF, McMurray JJ, Ahmed A. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail* 2013; **15**: 551–559.
 23. Ahmed A, Pitt B, Rahimtoola SH, Waagstein F, White M, Love TE, Braunwald E. Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. *Int J Cardiol* 2008; **123**: 138–146.
 24. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016; **50**: e1–e88.
 25. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015; **351**: h4451.
 26. Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, Ridefelt P, Lawrence JH, De Caterina R, Vinereanu D, Hanna M, Flaker G, Al-Khatib SM, Hohnloser SH, Alexander JH, Granger CB, Wallentin L. Digoxin and mortality in patients with atrial fibrillation. *J Am Coll Cardiol* 2018; **71**: 1063–1074.
 27. Zhou HB, An DQ, Zhan Q, Liu ZH, Hua JH, Lai WY, Huang YL, Zeng QC, Xu DL. A retrospective analysis of clinical characteristics and outcomes of heart failure patients with different left ventricular ejection fractions. *Zhonghua Nei Ke Za Zhi* 2017; **56**: 253–257.
 28. Dokainish H, Teo K, Zhu J, Roy A, Al Habib KF, El Sayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanis F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Belle-Cote E, Balasubramanian K, Islam S, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Bangdiwala SI, Yusuf S. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health* 2017; **5**: e665–e672.
 29. Hai JJ, Chan PH, Huang D, Ho MH, Ho CW, Cheung E, Lau CP, Tse HF, Siu CW. Clinical characteristics, management, and outcomes of hospitalized heart failure in a Chinese Population—The Hong Kong Heart Failure Registry. *J Card Fail* 2016; **22**: 600–608.
 30. Chen JY. Analysis of 164 cases of hospital inpatient use of traditional Chinese medicine in combination with digoxin in our hospital. *Practical Pharmacy And Clinical Remedies*. 2014; **17**: 339–341.