Heart & Lung 48 (2019) 22–27

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Effect of digitalis level on readmission and mortality rate among heart failure reduced ejection fraction patients

Hassan Alkhawam, MD [a,b,1,*], Elsayed Abo-salem, MD [a,1], Feras Zaiem, MD [c], James Ampadu, MD [a], Aleef Rahman, MPH [d], Samian Sulaiman, MD [e], Anwar Zaitoun, MD [f], Tarek Helmy, MD [a], Timothy J. Vittorio, MD [g]

[a] Center for Comprehensive Cardiovascular Care, St Louis University, St Louis, MO, United States
[b] Department of Medicine, Icahn School of Medicine at Mount Sinai (Elmhurst), Elmhurst, NY, United States
[c] Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, United States
[d] School of Medicine, St. George's University, St. George's, Grenada
[e] Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, United States
[f] Division of Cardiology, Saint John Hospital and Medical Center, Detroit, MI, United States
[g] Bronx-Lebanon Hospital Center, Bronx, NY, United States

ARTICLE INFO

Article history:
Received 14 March 2018
Received in revised form 6 July 2018
Accepted 11 July 2018
Available online 30 August 2018

Keywords:
Digitalis
Readmission
Heart failure
Mortality
Ejection fraction
Cardiomyopathy

ABSTRACT

Introduction: Digitalis has been used for over 200 years to treat patients with heart failure, and evidence supports its use to improve clinical symptoms and quality of life, but not survival. The objective of this retrospective study was to evaluate the effects of digitalis on readmission and mortality in patients with heart failure with reduced ejection fraction (HFrEF) who were receiving current guideline recommended medical therapy.
Methods: We reviewed medical record data from a retrospective cohort study of 1047 patients admitted to the hospital from 2005 to 2014 with decompensated HFrEF. 244 received digitalis, at some point during patient trajectory, and 803 never received digitalis. The primary outcomes of interest were the length of stay in hospital, readmission rates after discharge at 1, 6, 12, and 24 months and the overall mortality rate, at the same time points.
Results: We studied the effects of digitalis after adjusting for age, sex, race, potentially confounding comorbidities, and prescription medications. Digitalis treatment is associated with decreases in EF in patients with HFrEF (OR = −2.83, $P < 0.001$) and was associated with an increased readmission rate for any reason after discharge from the hospital at 6, 12, and 24 months, 53%, 34%, and 35%, respectively. No statistically significant difference was found between patients who received digitalis and those who did not (referent group) for the length of hospital stay and overall mortality rate.
Conclusion: Digitalis use is associated with increased re-admission rates for any reason following discharge from the hospital at 6, 12, and 24 months.

Background

Heart failure (HF) syndrome is a major health problem associated with significant morbidity, mortality, and healthcare-related costs.[1] The goals of HF-therapy are to improve symptoms, and quality of life and reduce mortality. The American College of Cardiology/American Heart Association and the European Society of Cardiology[2] recommend initial therapy for heart failure with reduced ejection fraction (HFrEF) with diuretics, Renin-Angiotensin-Aldosterone system blockers and B-blockers. Additional therapies among HFrEF, such as digitalis, are recommended in selected patients such as symptomatic patients with stage C or D HF, or as a second line therapy for controlling the heart rates of patients with atrial fibrillation with HFrEF.

Digitalis, a drug derived from nearly 20 species foxgloves, has been used for over 200 years to treat patients with HF.[3] This cardiac glycoside has a positive inotropic effect by inhibiting the Na-K-ATPase pump in myocardial cells and a negative chronotropic effect

Abbreviations: ACEIs, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin-receptors blockers; LV, Left ventricle

The study is a single center retrospective study of patients who were admitted to Elmhurst Hospital Center, NY between January 1st, 2005 and December 31st, 2014 (Fig. 1). This study was approved by Institutional Review Board of the Mount Sinai School of Medicine.

* Corresponding author at: Center for Comprehensive Cardiovascular care, St Louis University, 3635 Vista Ave., 13th floor, St. Louis, MO 63110, United States.
E-mail address: alkhawamh@slu.edu (H. Alkhawam).

[1] Dr. Alkhawam and Abo-Salem are co-first authors.

https://doi.org/10.1016/j.hrtlng.2018.07.006
0147-9563/$ - see front matter © 2018 Elsevier Inc. All rights reserved.

by increasing parasympathetic tone.[4,5] Small clinical trials[6-9] showed that digitalis improved short-term hemodynamics and long-term outcomes, such as clinical symptoms and quality of life in patients with HFrEF.

Earlier RCTs from the 1990s, which predate the era of recommendations to prescribe beta blockers and ACEIs/ARBs, showed that withdrawal from digitalis, as opposed to digitalis use, resulted in deterioration of LV ejection fraction.[10-13] The Digitalis Investigator's Group (DIG) concluded with a randomized, placebo-controlled trial[14] that digitalis had no effect on overall mortality, but decreased the overall number of hospitalizations attributable to worsening heart failure in patients receiving optimal medical therapy. Digitalis use in the United States had declined significantly between 1997 and 2001. This was likely attributed to the negative results of the DIG trial which showed that digitalis did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure and the advent of new agents that conferred a mortality benefit, such as ACE inhibitors, beta blockers, and aldosterone antagonists.[15] A recent small randomized, placebo-controlled crossover trial showed that withdrawal from digoxin treatment did not lead to a reduction in ejection fraction.[16]

In this retrospective cohort study, we evaluated the effects of digitalis use on the length of stay in hospital, readmission rates after discharge at different time points and the overall mortality rate in a real-world population of HFrEF patients.

Method

Study design

The study is a single center retrospective study of patients who were admitted to a tertiary hospital; between January 1, 2005 and December 31, 2014 (Fig. 1). The annual inpatient admissions to our hospital estimated around 20,000–25,000, of which Heart failure admissions represent 15% of total hospital admissions. This study was approved by Institutional Review Board of the Electronic medical record chart analysis was done using QuadraMed Computerized Patient Record software.

We included the data from adult patients >18 years of age, who were admitted with a primary diagnosis of acute on chronic heart failure, had transthoracic echocardiography (TTE) within 12 months prior to admission, and were on prescribed digoxin. TTE was interpreted by an independent cardiologist. The echocardiogram report of each patient was reviewed and analyzed to extract the necessary information. Only Cases with HFrEF, defined as left ventricular EF ≤40%, and a therapeutic serum digoxin level (0.6–0.9 ng/ml) were included.[17]

The primary outcomes were the length of hospital stay, the readmission rate for any reason at 1, 6, 12, 24 months after discharge and the overall mortality rate at the same time points.

Echocardiography

The transthoracic echocardiogram was considered to reflect the level of systolic function if it was obtained within the last 6 months of the admission. 2D Echocardiograms were performed according to the recommendations of the American Society of Echocardiography. We assessed the ejection fraction by using the Biplane Simpson's method. Patients with EF ≤40% were included in our study.

Statistical analysis

Statistical analysis was performed by statistical software SPSS (IBM Corporation, USA) and $P < 0.05$ was considered significant.

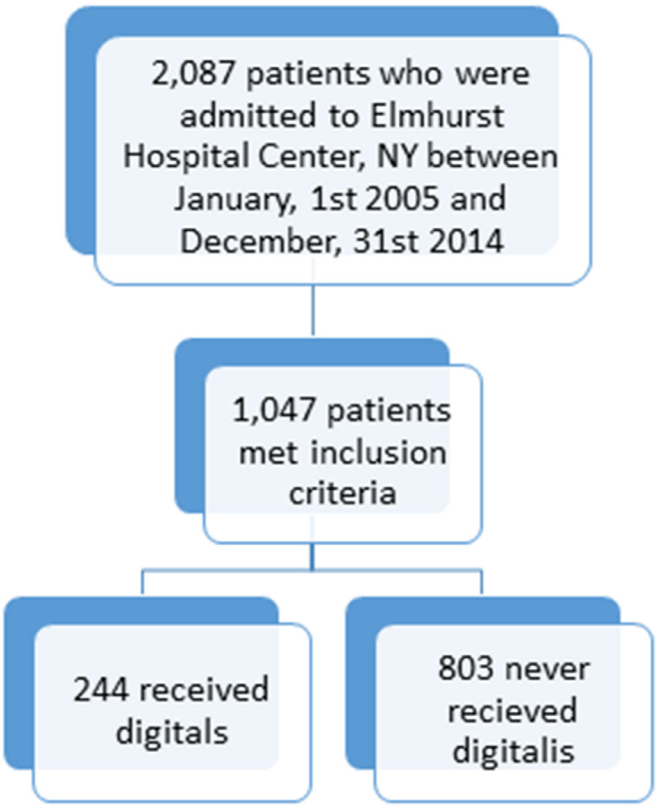

Fig. 1. Study flow diagram.

Chi-square, odds ratios and multivariate logistical regressions, time-to-event analysis using Kaplan-Meir plots and Cox proportional hazards modeling were used for the statistical analysis. We evaluated the medical records to determine the presence of hypertension, diabetes mellitus, obesity, dyslipidemia, tobacco use, chronic kidney disease (CKD), congestive heart failure (CHF) and gender. We determined CKD using the Cockcroft-Gault equation and included patients with CKD stage 3 and worse as a defining factor. Dyslipidemia was defined as low-density lipoprotein cholesterol of 130 mg/dL or greater or total cholesterol >200 mg/dL. Hypertension was defined as blood pressure 140/90 mm Hg or greater in two different setting. Lastly, diabetes mellitus was defined as having fasting blood glucose levels greater than or equal to 126 mg/dL or by having a hemoglobin A1C level greater than or equal to 6.5%.

Results

We identified 2087 patients who were admitted to the hospital from 2005 to 2014 with acute on chronic decompensated heart failure. A total of 1047 patients had HFrEF, 244 patients received digitalis treatment within in the therapeutic range, compared to 803 patients who did not receive digitalis therapy (Fig. 1). Baseline characteristics of the patients are listed in Table 1. The average age was 66 (SD ± 2.6) years and 68% (SD ± 3.2) were male. There was a significant racial discrepancy among groups; African American and Hispanic patients were more likely to receive digitalis compared to Caucasian patients. Patients receiving digitalis were more likely to have atrial fibrillation (AF) and lower ejection fraction, but were less likely to have chronic kidney disease (Table 1).

Table 1
Clinical and Demographic Characteristics of the Sample at Baseline in the non-digitalis vs. digitalis groups

Variable	Non-digitalis group (*N* = 803)	Digitalis group (*N* = 244)	*P* value
Age (years); mean (SD)	66.07 (14.7)	65.30 (14.8)	0.48
Males; % (*n*)	68.88% (529)	68.85% (168)	0.39
Race	<0.001		
White; % (*n*)	29.14% (234)	22.13% (52)	0.02
African American; % (*n*)	18.18% (146)	19.67% (47)	0.7
Hispanic; % (*n*)	16.56% (133)	26.23% (62)	0.002
Other; % (*n*)	35.7% (287)	31.2% (76)	0.2
Comorbidities			
Hypertension; % (*n*)	33.7% (271)	30% (75)	0.38
DM; % (number)	29.1% (234)	28.7 (70)	0.89
Hyperlipidemia; % (*n*)	71.5% (574)	69.7% (170)	0.58
CAD; % (number)	57.04% (458)	61.07% (149)	0.26
CKD (≥stage 3); % (*n*)	24.9% (220)	4.1% (10)	<0.001
NYHA class III or IV; % (*n*)	73.97 (594)	71.7% (175)	0.49
AICD	301 (37.5%)	92 (37.7%)	0.87
Atrial fibrillation; % (*n*)	17.3% (139)	37.7% (92)	<0.001
Medications			
Beta-blocker; % (*n*)	87.42% (702)	88.93% (217)	0.53
Lasix; % (*n*)	86.43% (694)	91.39% (223)	0.04
ACE-I; % (*n*)	65.88% (529)	67.21% (164)	0.70
Statin; % (*n*)	73.10% (587)	64.75% (158)	0.01
ARB; % (*n*)	14.82% (119)	17.21% (42)	0.36
Ejection fraction	26.79%	23.85%	<0.001

CKD, chronic kidney disease, ACE-I, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

Average length of stay was longer for the digitalis group (6.3 days) than the non-digitalis group (5.8 days), but the difference was not statistically significant. The readmission rate to the hospital for any reason was 16.5% at 1 month after discharge and increased steadily until 47.3% at 2 years. A higher readmission rate was observed in the digitalis group at all time-points (1, 6, 12, and 24 months). However, the difference was statistically significant only at 6, 12, and 24 months (Table 2).

Overall mortality rate was 3% at 1 month and increased gradually up to 4% at 12 months and 5% at 24 months. Short-term mortality rate, at 1 and 6 months, was higher in the non-digitalis group while long-term mortality rate, 12 and 24 months, was higher in digitalis group. None of these differences were statistically significant (Table 2 and Fig. 2).

We studied the effect of digitalis on the outcomes of interest between the two groups after adjusting for age, gender, race and prescription medications. Patients who were on digitalis treatment found to have a statistically significant lower EF among HFrEF group (OR= −2.83, $P < 0.001$). Digitalis group found to have a non-statistically significant shorter stay at hospital (OR = 0.48, $P = 0.43$) by almost 2 days (Table 3). Additionally, digitalis was associated with a higher rate of readmission rate for any reason by 37%, 53%, 34%, and 35% at 1, 6, 12, and 24 months after discharge, respectively. However, the difference between the groups with and without digitalis was statistically significant at all time-points except at 1 month. Use of digitalis was associated with an increased mortality rate by 3%, 27%, 39%, and 29% at 1, 6, 12, 24 months. However, the differences between the two groups in these rates were not statistically significant (Table 3 and Fig. 3).

Table 2
Comparison of outcomes in the digitalis vs. the non-digitalis groups.

Variable	Digitalis group (*N* = 244)	Non-digitalis group (*N* = 803)	*P* value
Ejection fraction	23.85 (8.56)	26.10 (8.57)	<0.001*
Length of stay (days)	6.26 (7.87)	5.78 (7.07)	0.23
Readmission rate			
1 Month	21.31% (52)	17.67% (185)	0.09
6 Months	43.44% (106)	35.72% (374)	<0.001*
12 Months	48.36 % (118)	42.79% (448)	0.04*
24 Months	54.92% (134)	49.09% (514)	0.04*
Mortality rate			
1 Month	2.87% (7)	2.96% (31)	0.92
6 Months	3.28% (8)	2.87% (30)	0.66
12 Months	5.33% (13)	4.39% (46)	0.42
24 Months	6.15% (15)	5.35% (56)	0.52

* $P < 0.05$, statistically significant; HFrEF, heart failure with reduced ejection fraction.

Subgroup analysis based on racial differences

There were not significant differences among the Caucasians between patients with or without digitalis therapy, in regard to readmission and mortality rates (Table 4). Among the Hispanic group, patients who were on digitalis had lower ejection fractions and higher 30-day, 6-month, and 1-year readmission rates compared to the Hispanic non-digitalis group (Table 5). Among the African American group, there was a non-significant trend for the digitalis group to lower ejection fractions, and lower 30-day, 6-month, and 1-year readmission rates, compared to the non-digitalis group (Table 6).

Subgroup analysis of atrial fibrillation

Out of 2087 patients with documented heart failure, 504 (24.9%) patients had atrial fibrillation. Out of 504 patients, 231 (64.1%) patients had HFrEF and atrial fibrillation. Among the 231 patients with atrial fibrillation, 39.8% were taking prescribed digitalis versus 60.2% who were not. Patients who were on digitalis had higher 6-month readmission rates but no different 30-day and 1-year readmission rates. Although there was a trend suggesting a lower ejection fraction n the digitalis group, it was not statistically significant (Table 7).

Discussion

In this retrospective cohort study, we evaluated the effect of digitalis use on length of hospitalization, readmission rates, and overall mortality in patients with HFrEF. In order to improve generalizability, we included subjects with varying ethnic backgrounds that were established on guideline-directed medical therapies. We also included subjects with common co-morbidities that were not assessed in the Digitalis Investigation Group trial such as atrial fibrillation. However, some of these results were demonstrated over twenty years ago by the Digitalis Investigation Group and lead one to question whether they can be replicated in this present age.[14]

Out of 1047 hospitalized patients with HFrEF, 23.3% of the patients were on digitalis treatment that was maintained in the therapeutic range and 76.7% had never received digitalis. Length of hospital stay and overall mortality at 1, 6, 12, and 24 months were not statistically significant between the groups. However, when comparing all-cause hospital readmissions at 6, 12, and 24 months, digitalis treatment was associated with an increased hospital readmission rate of 53%, 34%, and 35% respectively.

After analyzing the study population by ethnicity, there were notable differences with digitalis treatment. Caucasians made up nearly 30% of the study population and on average were the oldest ethnic group studied. Among this group, there were no significant differences in readmissions or mortality with digitalis compared to the control. African Americans made up nearly 20% of the study population and on average were the youngest ethnic group studied. Among this group, it was noted

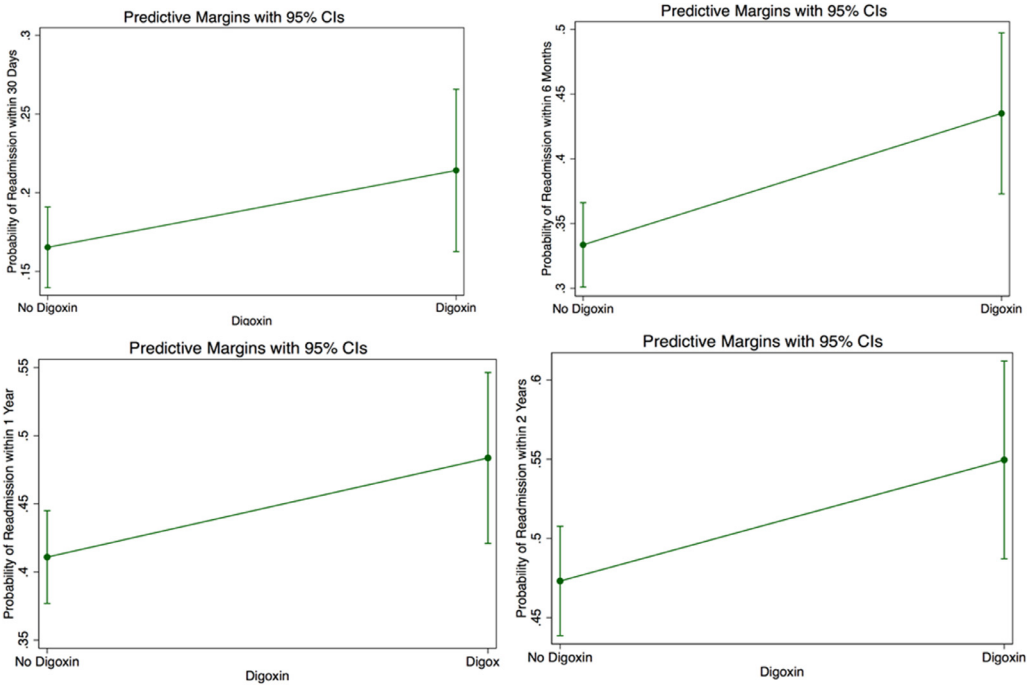

Fig. 2. Probability of mortality between Digitalis Treatment Groups; predictive margins with 95% CI. (A) 1 month; (B) 6 months; (C) 12 months; (D) 24 months.

Table 3
Adjusted logistic and multilinear regression model of HFrEF in digitalis group vs. non-digitalis group; odds ratio and 95% confidence intervals.

Variable	Digitalis vs. non-digitalis group	*P* value
	OR (95% CI)	
Ejection fraction	−2.83 (−4.03, −1.63)	<0.001*
Length of stay (days)	0.48 (−0.07, 0.16)	0.43
Readmission rate		
1 Months	1.37 (0.96, 1.97)	0.08
6 Months	1.53 (1.14, 2.06)	<0.001*
12 Months	1.34 (1.00, 1.79)	0.04*
24 Months	1.35 (1.01, 1.81)	0.04*
Mortality rate		
1 Month	1.03 (0.43, 2.46)	0.93
6 Months	1.27 (0.55, 2.93)	0.57
12 Months	1.39 (0.71, 2.73)	0.33
24 Months	1.29 (0.69, 2.41)	0.42

* $P < 0.05$, statistically significant; CI, confidence interval; OR, odds ratio.

that the choice of digitalis treatment was utilized on the lowest ejection fraction patients but without any statistically significant difference in readmission rates or mortality. However, among the African American group, the digitalis group had lower ejection fraction, and lower 30-day, 6-month, and 1-year readmission rates comparing to non-digitalis group. This was not statistically significant because of the sample size in this study but digitalis may provide potential benefit in this racial group. Hispanics also made up nearly 20% of the study population and similarly, the choice of digitalis treatment in Hispanics was utilized on the lowest ejection fraction patients. This group was also noted to have the worst outcomes with digitalis treatment. They experienced higher readmissions at all specified time periods, 1, 6, and 12 months. At one month, 33% of Hispanic patients were readmitted. At one year, over 60% of Hispanic patients had been readmitted. There was a significant racial discrepancy among ethnic groups in our study; African American and Hispanic patients were more likely to receive digoxin compared to Caucasian patients and treatment was favored on the lowest ejection fraction non-Caucasian patients. In the Digitalis Investigation Group trial, only 14% of the study population was of non-white race. Moreover, these subjects had a higher average ejection fraction, with the large majority of heart failure consisting of an ischemic origin. With such contrasting data and the plausibility of potential harm, further trials are needed in these specific populations of HFrEF prior to initiation of digitalis.

Our results are contradictory to the preexisting data described in the Digitalis Investigation Group trial. This may be secondary to the characteristics of the patients included in our study. More than 70% of the study patients were in NYHA class III or IV, with an average ejection fraction of ~24% in the treatment arm. Nearly 40% of the digitalis treatment group had a diagnosis of atrial fibrillation, which was excluded in the former digitalis trials. Finally, almost 90% of our patients were receiving treatment with beta blockers prior to the initiation of digitalis. These variables not only represent a common patient with HFrEF in current practice, but they depict a more complex, debilitated patient.

Our study magnifies the complexity and composition of today's HFrEF patient. It ignites inquisition if one size truly fits all when it comes to therapies for these patients. Genetic polymorphisms have been described to play a major role in the variability of drug responses in different races, potentially altering pharmacokinetics and specific drug targets. By evaluating outcomes of digitalis use in Caucasians, African Americans, and Hispanics, our study provides the first data to suggest genetic variability with digitalis use in patients with HFrEF. With this data and the potential for harm, further trials evaluating digitalis are needed in these specific populations to effectively reduce hospitalizations, readmissions, and healthcare cost. With continued investigation on genetic polymorphisms in digitalis, management of the morbidity and potentially mortality that comes with HFrEF may improve in certain sub-populations. Finally, our study did not find harm in utilizing digitalis in patients with HFrEF and concomitant atrial fibrillation. As many patients with HFrEF also have atrial fibrillation, digitalis can be a reasonable option in managing these common co-morbidities.

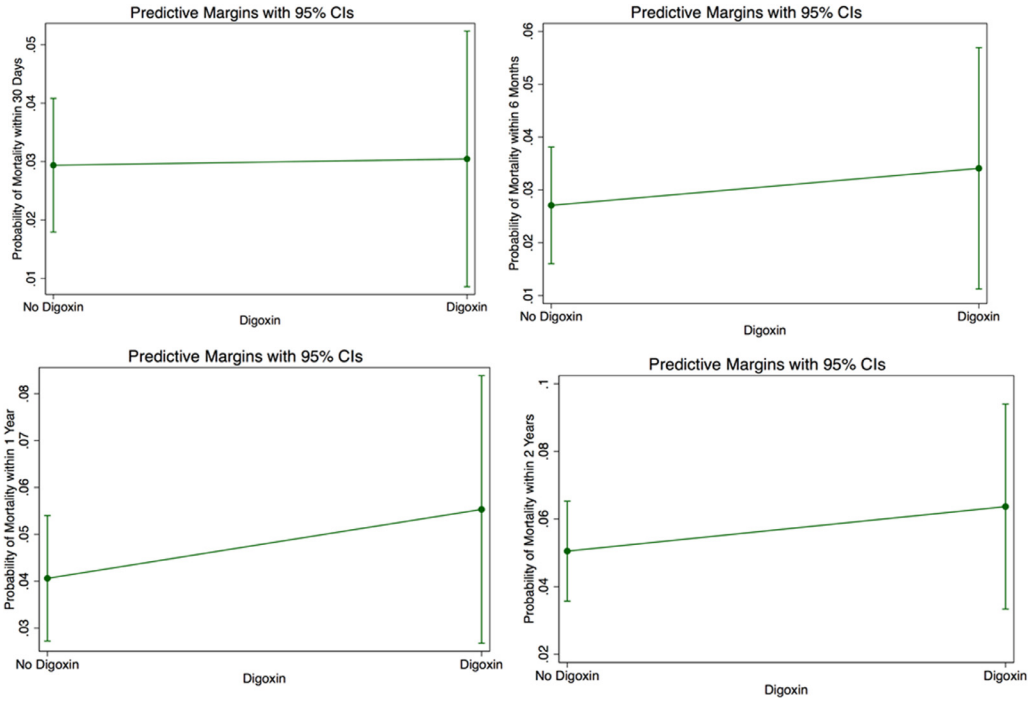

Fig. 3. Probability of readmission between Digitalis Treatment Groups; predictive margins with 95% CI. (A) 1 month; (B) 6 months; (C) 12 months; (D) 24 months.

Table 4
Comparison outcomes of the digitalis vs. non-digitalis Caucasian group.

	Digitalis group $n = 52$	Non-digitalis group $n = 234$	Statistics
Average age	72-year-old	71.39-year-old	$P = 0.7$
Average EF	25.29	26.45	$P = 0.39$
30-days readmission	11 (21.2%)	41 (17.5%)	OR: 1.26 95% CI: 0.6–2.6 $P = 0.53$
6 months readmission	23 (44.2%)	81 (34.6%)	OR: 1.5 95% CI: 0.8–2.7 $P = 0.2$
1-year readmission rate	26 (50%)	106 (45.3%)	OR: 1.2 95% CI: 0.7–2.2 $P = 0.5$
Length of stay	5.7 days	6.5 days	$P = 0.4$
Mortality rate	6 (11.5%)	13 (5.5%)	OR: 2.2 95% CI: 0.8–6.14 $P = 0.12$

Table 5
Comparison outcomes of the digitalis vs. non-digitalis Hispanic group.

	Digitalis group $n = 62$	Non-digitalis group $n = 133$	Statistics
Average age	67.27	64.56	0.2
Average EF	24.6	28.21	$P = 0.004$
30-days readmission	21 (33.9%)	23 (17.3%)	OR: 2.4 95% CI: 1.2–4.9 $P = 0.01$
6 months readmission	37 (59.7%)	38 (28.6%)	OR: 3.7 95% CI: 2–7 $P < 0.0001$
1-year readmission rate	38 (61.3%)	48 (36.1%)	OR: 2.8 95% CI: 1.5–5.2 $P = 0.001$
Length of stay	9 days	5.2 days	$P = 0.3$
Mortality rate	1 (1.6%)	7 (5.3%)	OR: 0.3 95% CI: 0.04–2.4 $P = 0.3$

Table 6
Comparison outcomes of the digitalis vs. non-digitalis African American group.

	Digitalis group $n = 47$	Non-digitalis group $n = 146$	Statistics
Average age	59.5	57.4	0.35
Average EF	21.2%	25.4%	0.001
30-days readmission	4 (8.5%)	24 (16.4%)	OR: 0.5 95% CI: 0.2–1.4 $P = 0.2$
6 months readmission	14 (29.8%)	49 (33.6%)	OR: 0.8 95% CI: 0.4–1.7 $P = 0.63$
1-year readmission rate	15 (31.5%)	60 (41.1%)	OR: 0.7 95% CI: 0.3–1.3 $P = 0.3$
Length of stay	5 days	5.7	0.41
Mortality rate	1 (2.1%)	1 (0.68%)	OR: 3.2 95% CI: 0.2–51.4 $P = 0.4$

Table 7
Comparison of outcomes of the digitalis vs. non-digitalis in atrial fibrillation group.

	Digitalis group $n = 92$	Non-digitalis group $n = 139$	Statistics
Average age	70.9-year-old	71.8-year-old	$P = 0.62$
Average EF	25.4%	27.7%	$P = 0.07$
30-days readmission	22 (23.9%)	30 (23.02%)	OR: 1.1 95% CI: 0.6–2.1 $P = 0.7$
6 months readmission	42 (45.7%)	45 (32.4%)	OR: 1.8 95% CI: 1.019–3.02 $P = 0.04$
1-year readmission rate	45 (48.9%)	55 (39.6%)	OR: 1.5 95% CI: 0.9–2.5 $P = 0.16$
Length of stay	7.0 days	7.4 days	0.74
Mortality rate	4 (4.3%)	4 (2.9%)	OR: 1.5 95% CI: 0.4–6.3 $P = 0.6$

Limitations

This study was retrospective and causality cannot be inferred. Although the baseline characteristics of both groups did not differ significantly (except for CKD, racial difference, use of statins and use of Torsemide), the selection bias effect cannot be completely eliminated likely because residual confounders might not be apparent and difficult to control.[13]

Conclusion

Digitalis is associated with increased re-admission rates for any reason following discharge from the hospital at 6, 12, and 24 months. Length of hospital stay and overall mortality at 1, 6, 12, and 24 months were not statistically significant between the groups. Analysis based on racial group showed no outcome benefit for the Caucasian group, harm for the Hispanic group and potential benefit in the African American group. However, further investigation is needed to clarify these findings such as the racial variation outcomes among HFrEF and being treated with digitalis.

Disclosure

None.

Source of funding

None.

Acknowledgments

The abstract of this study was presented at Heart Failure society of America in Orlando, FL 09/2016.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hrtlng.2018.07.006.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10): e146–e603.
2. Ponikowski P, Voors AA, Anker SD, et al. 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 J Heart Fail*. 2016;18(8):891–975.
3. Withering W, Withering W. *An Account of the Foxglove, and Some of Its Medical Uses: With Practical Remarks on Dropsy, and Other Diseases*. Birmingham, London: Printed by M. Swinney for G.G.J. and J. Robinson; 1785:233.
4. McMahon WS, Holzgrefe HH, Walker JD, et al. Cellular basis for improved left ventricular pump function after digoxin therapy in experimental left ventricular failure. *J Am Coll Cardiol*. 1996;28(2):495–505.
5. Smith TW, Digitalis. Mechanisms of action and clinical use. *N Engl J Med*. 1988;318 (6):358–365.
6. Ribner HS, Plucinski DA, Hsieh AM, et al. Acute effects of digoxin on total systemic vascular resistance in congestive heart failure due to dilated cardiomyopathy: a hemodynamic-hormonal study. *Am J Cardiol*. 1985;56(13):896–904.
7. Gheorghiade M, St Clair J, St Clair C, et al. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. *J Am Coll Cardiol*. 1987 9(4):849–857.
8. Fleg JL, Rothfeld B, Gottlieb SH. Effect of maintenance digoxin therapy on aerobic performance and exercise left ventricular function in mild to moderate heart failure due to coronary artery disease: a randomized, placebo-controlled, crossover trial. *J Am Coll Cardiol*. 1991;17(3):743–751.
9. Lee DC, Johnson RA, Bingham JB, et al. Heart failure in outpatients: a randomized trial of digoxin versus placebo. *N Engl J Med*. 1982;306(12):699–705.
10. Adams Jr KF, Gheorghiade M, Uretsky BF, et al. Patients with mild heart failure worsen during withdrawal from digoxin therapy. *J Am Coll Cardiol*. 1997;30(1): 42–48.
11. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med*. 1993;329(1):1–7.
12. Uretsky BF, Young JB, Shahidi FE, et al. 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(4):955–962.
13. Ziff OJ, Kotecha D. Digoxin: the good and the bad. *Trends Cardiovasc Med*. 2016;26 (7):585–595.
14. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336(8):525–533.
15. Goldberger ZD, Alexander GC. Digitalis use in contemporary clinical practice: refitting the foxglove. *JAMA Intern Med*.. 2014;174(1):151–154.
16. Hopper I, Skiba M, von Lueder TG, et al. Digoxin withdrawal worsens clinical status in stable patients with heart failure receiving optimal contemporaneous therapy—a randomized controlled trial. *J Card Fail*. 2015;21(9):779–781.
17. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA*. 2003;289:871–878.