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Original Article

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Impact of Digoxin Use on Guideline-Directed Medical Therapy in Patients With Heart Failure With Reduced Ejection Fraction

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Abstract

Background: Digoxin was one of the first agents used in the management of heart failure with reduced ejection fraction (HFrEF). Concerns over its safety, efficacy, and the introduction of guideline-directed medical therapy (GDMT) have relegated it to a secondary role. The efficacy of digoxin is still under debate, and its use in patients on GDMT remains unclear. We aim to evaluate whether patients with HFrEF on digoxin can tolerate higher doses of a β-blocker (BB), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitor (ARNI).

Methods: A retrospective chart review was performed on 233 patients with HFrEF managed at a tertiary care center in Cleveland, Ohio. A bivariate analysis was performed to compare patients on digoxin with patients not on digoxin in terms of ability to progress the dosing of BB, ACEI, MRA, ARB, or ARNI.

Results: Thirty-four (14.6%) of our 233 patients were receiving digoxin at baseline visit. The digoxin group was more likely to have lower initial and last systolic blood pressure, initial diastolic blood pressure, and left ventricular ejection fraction. Mean follow-up duration and baseline sodium level were higher in the digoxin group. There was no significant difference between the two groups in terms of patients receiving higher doses of BB (P = 0.235), ACEI/ARB (P = 0.903), MRA (P = 0.331), or ARNI (P = 0.717).

Conclusions: There was no significant difference between the doses of BB, ACEI, ARB, MRA, or ARNI among HFrEF patients on digoxin compared to those that were not. Randomized control trials with a larger sample are needed to establish our findings of digoxin not significantly affecting the ability to up titrate GDMT in HFrEF patients.

Keywords: Guide-directed medical therapy; Digoxin; Heart failure with reduced ejection fraction

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Introduction

Heart failure is an increasing cause of death worldwide and is a growing economic and health burden in the United States [1]. For patients with heart failure who have reduced ejection fraction (HFrEF), guideline-directed medical therapy (GDMT) is considered the mainstay of management as per the recommendations of the American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) [2-6]. Pharmacologic GDMT consists of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitor (ARNI), β-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) given at the maximum tolerated dose [2].

For HFrEF patients who continue to have persistent symptoms despite GDMT (or who are unable to tolerate GDMT), digoxin is a class 2b recommendation to decrease hospitalization for heart failure [3, 4, 7]. The benefit of digoxin in GDMT remains unclear. Some studies have shown that digoxin has a positive effect on morbidity by decreasing hospitalization and improving patients' quality of life [8-10]. Other studies have shown that its use is associated with increased mortality [11-13].

It is well established that digoxin has positive inotropic effects; however, whether this could be utilized to advance GDMT in heart failure patients is not well established [14]. Consequently, we aimed to see if patients on digoxin can tol-

erate higher doses of BBs, ACEIs, ARB, or ARNI. We performed a retrospective chart review and compared the doses received by each group.

Materials and Methods

Study design and participants

The study was approved by the Institutional Review Board at a university hospital. The need for informed consent was waived because of the retrospective nature of the study using coded and anonymized data obtained from routine care. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects.

We conducted a retrospective observational study using data from patients with HFrEF managed at our GDMT Optimization Clinic in Cleveland, Ohio, USA. All patients who carried the diagnosis of HFrEF were identified in the study period from January 2017 to December 2019 and were screened for inclusion.

Inclusion criteria were age ≥ 18 years and having a diagnosis of heart failure and a left ventricular ejection fraction (LVEF) of ≤ 40% by echocardiography performed within 12 months. Patients were excluded if they only had one follow-up visit to the GDMT Optimization Clinic.

Variables were obtained by chart review from electronic medical records. For all patients, we collected the following data: age, gender, height, weight, diabetes mellites, tobacco use, hypertension, atrial fibrillation, chronic kidney disease (CKD), coronary artery disease (CAD), and depression. Moreover, baseline labs were also obtained: sodium, potassium, chloride, blood urea nitrogen (BUN), and creatinine.

Therapy characteristics and outcome measurements

The primary outcome is the effect of digoxin on GDMT. We split patients into two groups based on digoxin use at the baseline visit. Data regarding the use of GDMT such as BBs (metoprolol succinate, carvedilol, or bisoprolol), ACEI/ARB, MRA or ARNI were collected. Information regarding highest tolerated GDMT dose was collected. Medications were converted to equivalent dosages for lisinopril, carvedilol, or spironolactone to enable statistical analysis. Dosages were divided into minimum (< 50% of target dose), intermediate (50% of target dose) and maximum dose (full dose). Dose equivalents were based on approximate starting dose within each medication class based on ACC and the methods of Grewal et al [15, 16]. We divided equivalent doses as follows; metoprolol succinate 25 mg/day ≈ 6.25 mg/day carvedilol ≈ 2.5 mg bisoprolol daily. For ACEI/ARB the equivalent doses were as follows: captopril 18.75 mg/ day ≈ enalapril 2.5 mg/day ≈ ramipril 2.5 mg/ day ≈ lisinopril 5 mg/day ≈ candesartan 4 mg/day ≈ valsartan 40 mg/ day ≈ losartan 25 mg daily. Doses of spironolactone and eplerenone were considered equivalent. Target doses of carvedilol equivalents were 50 mg/day, lisinopril equivalents were 40 mg/day and spironolactone equivalents were 25 mg/day. For the ARB-ARNI combination (i.e., sacubitril-valsartan combination); 24/26 mg two times daily was considered the minimum dose, 49/51 mg two times daily moderate dose, and two times daily 97/103 mg as the maximum dose. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors were not recommended as part of GDMT at the time of the current study. Moreover, hydralazine, isosorbide dinitrate, and ivabradine were not included due to low prescription rates and more specialized indications for these medications.

Statistical analysis

Categorical variables are expressed as numbers and percentages. Data with normal distributions are reported as mean and standard deviation (SD) and data without a normal distribution as a median and interquartile range (IQR, 25 - 75). Treatment effects were assessed by comparisons between groups, and analyses of all available data were carried out according to baseline visit assignments (by the intention-to-treat principle). We use *t*-test to compare continuous variables and Chi-square for categorical variables between two groups. A bivariate analysis was performed to compare patients on digoxin with patients not on digoxin in terms of ability to progress the dosing of BB, MRA, and ACEIs/ARB or ARNI. All statistical analysis was carried out using R version 3.6.2.

Results

During the study period, we identified 233 patients who met our inclusion and exclusion criteria; 14.6% of the population had received digoxin. Three patients (8.82%) from the digoxin group had stopped digoxin during the follow-up period and three patients (1.51%) from the non-digoxin group started taking digoxin during the follow-up period. The average age was 64 (SD 15) for patients on digoxin and 60.1 (SD 16.1) for patients not on digoxin (P = 0.78), and the male to female ratio was 2:1 and 5:3, respectively (P = 0.33). The mean duration of the last follow-up visits for all subjects was 221.8 (SD 125.7) days. Both cases and controls had similar patient characteristics, with the exception of follow-up duration and the LVEF (Table 1). When we compared baseline and last visit vitals and biochemical testing; baseline systolic and diastolic blood pressure, last visit systolic blood pressure and baseline sodium level were lower in the digoxin group (Table 2).

There was no significant difference in the proportion of patients receiving higher doses of BBs (P = 0.235), ACEI/ARB (P = 0.903), MRA (P = 0.331), or ARNIs (P = 0.717) between the two groups (Table 3).

Discussion

Digoxin was one of the first used medications to treat heart failure. The majority of the data regarding digoxin use in HFrEF comes from meta-analyses of retrospective studies, in addition to randomized controlled trials such as DIG, RADI-

Table 1. Baseline Characteristics and Comorbidities

	Digoxin (n = 34)	Without digoxin (n = 199)	P value
Age (years)	64 (± 15.0)	60.1(±16.1)	0.19
Female	12 (35.3%)	76 (38.2%)	0.33
Race			0.24
White	21 (61.8%)	126 (63.3%)	
Blacks	9 (26.5%)	37 (18.6%)	
Others	4 (11.8%)	3 (18.1%)	
Weight	98 (67 - 110)	93 (73 - 113)	0.35
Height	165 (160 - 176)	164 (160 - 167)	0.27
Tobacco use (active/former)	22 (64.7%)	115 (57.8%)	0.45
DM	13 (38.2%)	84 (42.2%)	0.65
Hypertension	26 (76.5%)	167 (83.9%)	0.89
Atrial fibrillation	23 (67.7%)	144 (72.4%)	0.78
CKD	15 (44.1%)	53 (26.6%)	0.89
CAD	14 (41.2%)	35 (17.6%)	0.76
Depression	5 (14.7%)	14 (7.0%)	0.44
NYHA			0.41
Class I - II	13 (38.2%)	90 (48.1%)	
Class III - IV	21 (61.8%)	97 (51.9%)	
LV ejection fraction	22.5 (± 9.2)	26.3 (± 8.7)	0.02
Follow-up duration, days	272.2 (± 116.9)	213.2 (± 125.4)	0.01

The threshold of significance is P < 0.05. ±: standard deviation. CKD: chronic kidney disease; CAD: coronary artery disease; DM: diabetes mellites; NYHA: New York Heart Association Functional Classification; LV: left ventricular.

ANCE, and PROVED [10, 17, 18]. The authors of the DIG trial found that digoxin reduced heart failure-related hospitalizations in HFrEF, but it did not affect mortality or quality of life. However, this trial was performed at a time when GDMT use had not been established [19, 20]. Since then, many observational studies have shown similar results that while digoxin decreased patient symptoms and readmissions, it lacked mortality or even increased mortality [10, 21].

A *post hoc* analysis of the DIG trial showed a serum digoxin concentration of 0.5 - 0.9 ng/mL was associated with reduced all-cause mortality and HF hospitalizations [22]. Current 2022 ACC/AHA/HFSA guidelines recommend initiation of digoxin in patients after optimization of GDMT or in patients who cannot tolerate GDMT in the absence of any contraindications [3]. There has been a scarcity of randomized control trials answering critical questions about the role of digoxin in today's clinical practice and their interactions with current GDMT, except for the RATE-AF trial [23]. This randomized clinical trial of atrial fibrillation patients showed improved heart failure and atrial fibrillation-related symptoms in those taking digoxin in

Table 2. Labs and Vitals for First and Last Visit

Variable	First visit			Last visit		
	Digoxin (n = 34)	Without digoxin (n = 199)	P value	Digoxin (n = 34)	Without digoxin (n = 199)	P value
HR (bpm)	75.2 (± 12.8)	77.9 (± 14.4)	0.331	74.3 (± 11.5)	73.5 (± 13)	0.79
SBP (mm Hg)	110.8 (± 15.4)	123.1 (± 18.8)	< 0.01	110.9 (± 16.3)	118.1 (± 17.6)	0.03
DBP (mm Hg)	65.4 (± 11.8)	71.6 (± 12.9)	0.01	66.6 (± 11.7)	66.9 (± 11.7)	0.89
Sodium (mmol/L)	137 (± 2.6)	138 (± 3.2)	0.01	138.2 (± 2.7)	138.6 (± 2.8)	0.56
Potassium (mmol/L)	4.2 (± 0.36)	4.3 (± 0.56)	0.49	4.5 (± 0.49)	4.69 (± 3.5)	0.81
BUN (mg/dL)	29.36 (± 19.3)	26.9 (± 18.63)	0.49	33.7 (± 22)	28 (± 22.1)	0.26
Creatinine (mg/dL)	1.3 (± 0.69)	1.4(± 1)	0.81	1.3 (± 0.38)	1.4 (± 0.79)	0.69

The threshold of significance is P < 0.05. ±: standard deviation. HR: heart rate; bpm: beat per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; BUN: blood urea nitrogen.

Table 3. Bivariate Analysis Comparing Highest Tolerated Doses Guideline-Directed Medical Therapy Between Patients With HFrEF on Digoxin and Those not on Digoxin

	Digoxin (n = 34)		Without digoxin (n = 199)		P value
	First visit	Last visit	First visit	Last visit	
β-blocker dose					0.235
None	1 (2.9%)	1 (2.9%)	13 (6.5%)	4 (2%)	
Minimum	23 (67.6%)	15 (44.1%)	102 (51.3%)	66 (33.2%)	
Intermediate	3 (8.8%)	9 (26.5%)	51 (25.6%)	42 (21.1%)	
Maximum	7 (20.6%)	9 (26.5%)	33 (16.6%)	87 (43.7%)	
ACEI/ARB dose					0.903
None	16 (47%)	26 (76.5%)	113 (56.8%)	153 (76.9%)	
Minimum	13 (38.2%)	4 (11.8%)	56 (28.1%)	21 (10.6%)	
Intermediate	5 (14.7%)	2 (5.9%)	21 (10.6%)	16 (8%)	
Maximum	0	2 (5.9%)	9 (4.5%)	9 (4.5%)	
ARNI dose					0.717
None	20 (58.8%)	8 (23.5%)	116 (58.3%)	68 (34.2%)	
Minimum	5 (14.7%)	7 (20.6%)	51 (25.6%)	26 (13.1%)	
Intermediate	5 (14.7%)	7 (20.6%)	24 (12.1%)	31 (15.6%)	
Maximum	4 (11.8%)	12 (35.3%)	8 (4%)	74 (37.2%)	
MRA					0.331
None	26 (76.5%)	21 (61.8%)	135 (67.8%)	96 (48.2%)	
Intermediate	3 (8.8%)	5 (14.7%)	15 (7.5%)	31 (15.6%)	
Maximum	5 (14.7%)	8 (23.5%)	49 (24.6%)	72 (36.2%)	

The threshold of significance is $P < 0.05$. ±: standard deviation. ACEIs: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist.

comparison to bisoprolol. Further studies into the potential interactions between digoxin and GDMT are essential.

Previous literature also showed that HFrEF patients who were previously maintained on digoxin had an increased risk of heart failure and all-cause readmissions when digoxin was discontinued [24]. The combined risk of heart failure readmission and all-cause mortality was higher in the digoxin discontinuation group at all stages in follow-up. Hence, we investigated the question of whether the addition of digoxin correlates with additional dosing of GDMT. To our knowledge, there are no studies that have evaluated a similar outcome when it comes to digoxin use. One of the rationales supporting this idea was that the positive inotropic effect of digoxin would allow the patients to tolerate higher doses of GDMT medications which could help explain the symptom relief and reduction of readmissions shown in other studies [21]. Interestingly the effect of digoxin on inotropy and blood pressure could potentially be extrapolated from the RADIANCE trial as withdrawal of digoxin resulted in lower ejection fraction (EF) and systolic blood pressure [17].

Providers are hesitant when it comes to prescribing digoxin in CKD patients as it is cleared through the kidneys and higher serum concentrations have been associated with worse outcomes [25]. Interestingly we did not notice a statistically significant difference in diagnosis of CKD and baseline creatinine in those on digoxin and those not taking digoxin. This potentially may indicate that renal function did not play a significant factor in providers choosing to utilize digoxin in our sample.

Our results show that there was no significant difference in the maximally tolerated dose of BB, ACEI, ARB, or ARNI between patients receiving digoxin and patients who were not receiving digoxin. Hence, our study shows that digoxin administration in HFrEF patients does not allow for higher dosing of any of the individual components in the current GDMT. Given the lack of benefit of the addition of digoxin to increased dosing of any of the individual components of GDMT, our study does not support the initiation of digoxin before optimization of HF GDMT. Our study is prone to selection bias and differences in baseline blood pressure between both groups could potentially explain why the up-titration of GDMT was not statistically significant in the digoxin group. Moreover, digoxin tends to be used in patients with more severe and symptomatic heart failure which would probably also prevent other medications from being optimized [26]. The results of our study will need to be validated in an adequately powered randomized control trial.

Limitations

This study has limitations. First, the retrospective observation-

al nature of this study is its main limitation. Second, the fact it is a single-center study limits its scientific rigor or external validity. Third, data were collected from electronic medical records and thus are prone to miscoding, and errors in data entry which may introduce potential errors were not accounted for. Fourth, information regarding patient-specific factors that limit GDMT such as intolerance of ACEI or ARB may have limited continuing therapy was not included. Moreover, data on digoxin serum levels was limited thus information on which patients were able to achieve therapeutic range is not available. Fifth, patients receiving digoxin may have characteristics that differ from those that did not, introducing potential bias. Sixth, our small sample size could potentially increase the likelihood of type II error skewing the results. Seventh, using the last visit for follow-up time introduces a heterogenous timepoint which may introduce bias.

Conclusions

Digoxin use as an add-on to GDMT is still under question. In this study, there was no difference in the maximum tolerated dose of BB, ACEIs/ARB, or ARNI between patients receiving and not receiving digoxin. This shows that the addition of digoxin did not allow patients to tolerate higher doses of GDMT medications. The use of digoxin in HFrEF treatment in addition to GDMT has not been assessed in a recent randomized control trial and further research is needed to gauge its efficacy and safety.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors do not have any conflict of interest or relationships to disclose.

Informed Consent

The need for informed consent was waived because of the retrospective nature of the study using coded and anonymized data obtained from routine care.

Author Contributions

Ahmad Jabri: hypothesis, data analysis, project leader, literature review, manuscript writing, editing and review; Laith Alhuneafat: data analysis, manuscript writing, editing and review, and submission; Zaid Shahrouri: manuscript editing and writing; Hani Hamade MD: data collection, manuscript editing and writing; Farhan Nasser: data collection, manuscript writing and literature review, Abdallah Rayan: manuscript editing; Mohammed Mhanna: manuscript editing; Ahmad Al Abdouh: manuscript editing; Faris Haddadin: manuscript editing; Kathir Balakumaran: project supervision and review.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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