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Digoxin and Reduction of Heart Failure Hospitalization in Chronic Systolic and Diastolic Heart Failure

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Abstract

In the Digitalis Investigation Group trial, digoxin-associated reduction in the combined end point of heart failure (HF) hospitalization or HF mortality was significant in systolic but not in diastolic HF. To assess whether this apparent disparity can be explained by differences in baseline characteristics and sample size, we used propensity score matching to assemble a cohort of 916 pairs of systolic and diastolic HF patients who were balanced in all measured baseline covariates. We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) of the effect of digoxin on outcomes separately in systolic and diastolic HF, at 2 years (protocol pre-specified) and at the end of 3.2 years of median follow up. HF hospitalization or HF mortality occurred in 28% and 32% of systolic (HR when digoxin was compared with placebo =0.85, 95% CI =0.67 to 1.08, p =0.188), and 20% and 25% of diastolic (HR =0.79, 95% CI =0.60 to 1.03, p =0.085) HF patients respectively receiving digoxin and placebo. At 2 years, HR for this combined end point were similar for systolic (0.72, 95% CI =0.55 to 0.95, p =0.022) and diastolic (0.69, 95% CI =0.50 to 0.95, p =0.025) HF. Digoxin also reduced 2-year HF hospitalization in both systolic (HR =0.73, 95% CI =0.54 to 0.97, p =0.033) and diastolic (HR =0.64, 95% CI =0.45 to 0.90, p =0.010) HF. In conclusion, as in systolic HF, digoxin was equally effective in diastolic HF, who constitutes half of all patients with HF, yet has few evidence-based therapeutic options.

Keywords

Digoxin; Heart Failure; Systolic; Diastolic; Morbidity; Mortality

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Clinical Trial Registration Information: Information on DIG dataset can be found at the following NHLBI website: <http://www.nhlbi.nih.gov/resources/deca/descriptions/dig.htm>

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With over one million hospitalizations each year, heart failure (HF) is the number one reason for hospital admission among population ≥ 65 years in the United States.¹ Nearly half of the five million HF patients have diastolic HF and these patients are as likely as systolic HF patients to be hospitalized for HF.^{2,3} HF hospitalization is associated with increased mortality, and risk of post-discharge mortality is similar in both systolic and diastolic HF.⁴ Yet, few interventions to reduce HF hospitalization have been tested in diastolic HF. In the Digitalis Investigation Group (DIG) trial, digoxin significantly reduced HF hospitalization in systolic HF (left ventricular ejection fraction {LVEF} $\leq 45\%$) in the main trial (n=6800), but not in diastolic HF (LVEF $>45\%$) in the ancillary trial (n=988).^{5,6} This disparity in the effect of digoxin has been attributed to the smaller sample size of the DIG ancillary trial and potential baseline differences between systolic and diastolic HF patients.^{2,7} However, this has never been systematically examined and may have contributed to a potential underuse of digoxin in diastolic HF.^{8,9} We examined the effect of digoxin on outcomes separately in propensity-matched systolic and diastolic HF patients of equal sample size.

Methods

We used a public-use copy of the DIG dataset obtained from the NHLBI. The rationale, design, and results of the DIG trial have been previously reported.⁵ Briefly, 7788 chronic HF patients in normal sinus rhythm were randomized to receive digoxin or placebo. These patients were recruited from 302 clinical centers in the US (186) and Canada (116) between 1991 and 1993. Patients with LVEF $\leq 45\%$ (n = 6800) were enrolled in the main trial and those with LVEF $>45\%$ (n = 988) were enrolled in the ancillary trial. Patients received 4 different daily doses of digoxin or matching placebo (0.125, 0.25, 0.375, and 0.5 mg).⁵ Most patients were receiving diuretics ($>80\%$) and an angiotensin-converting enzyme inhibitors ($>90\%$).

Our main outcome was the combined end point of HF hospitalization or HF mortality because it was the primary outcome of the DIG ancillary trial and was used as the basis of US Food and Drug Administration approval of digoxin. Since this combined end point was primarily driven by a reduction in HF hospitalization, we also examined that outcome separately. We analyzed the effect of digoxin on these outcomes both at study end and at 2 years of follow up. The 2-year analysis was pre-specified in the DIG protocol and was also the basis of FDA approval.^{10,11} Outcomes data were classified by DIG investigators who were blinded to the patient's study-drug assignment and were 98.9% complete.¹²

To ensure that the effect of digoxin in systolic and diastolic HF patients would not be in part due to differences in baseline characteristics between these 2 groups, we assembled a propensity-matched population in which 916 pairs of systolic and diastolic HF patients were balanced in all measured baseline covariates. We calculated propensity scores for diastolic HF for each patient using a non-parsimonious multivariable logistic regression model adjusting for all measured baseline covariates displayed in Figure 1.^{13,14} Absolute standardized differences of $<10\%$ for all measured covariates suggested inconsequential post-match imbalance.^{13,15,16}

Kaplan-Meier cumulative plots for digoxin and placebo were constructed and compared using log-rank statistics, separately for systolic and diastolic HF. Cox proportional-hazards models were used to compare the effects of digoxin on both outcomes. To determine if the effect of digoxin persisted despite baseline differences, we repeated our analyses in a cohort of 988 systolic HF patients, randomly selected from the 6800 patients in the main trial. All analyses were performed on an intention-to-treat basis, with 2-sided values of $p < 0.05$ considered significant, using SPSS 15 for Windows.¹⁷

Results

Imbalances in baseline characteristics between patients with systolic and diastolic HF in the original dataset, and balance achieved after propensity matching are displayed in Figure 1. Baseline patient characteristics between patients receiving digoxin and placebo for matched systolic and diastolic HF patients are displayed in Table 1. The effect of digoxin on the combined end point of HF hospitalization or HF mortality was similar among systolic (hazard ratio {HR} = 0.85, 95% confidence interval {CI} = 0.67 to 1.08, $p = 0.188$) and diastolic (HR = 0.79, 95% CI = 0.60 to 1.03, $p = 0.085$) HF (Table 2 and Figure 2a). There was no significant interaction between digoxin and LVEF, regardless whether it was used as a categorical (using a 45% cut-off; $p = 0.655$) or a continuous variable ($p = 0.991$). The effect of digoxin on HF hospitalization was also similar in both systolic (HR = 0.80, 95% CI = 0.62–1.03, $p = 0.079$) and diastolic (HR = 0.77, 95% CI = 0.57 to 1.03, $p = 0.074$) HF (Table 2 and Figure 2b), also without any interaction.

At the end of 2 years of follow up, the effect of digoxin on the combined end point was similar among systolic (0.72, 95% CI = 0.55 to 0.95, $p = 0.022$) and diastolic (0.69, 95% CI = 0.50 to 0.95, $p = 0.025$) HF and digoxin also reduced HF hospitalization in both systolic (0.73, 95% CI = 0.54 to 0.97, $p = 0.033$) and diastolic (0.64, 95% CI = 0.45 to 0.90, $p = 0.010$) HF (Table 3).

Among a random subset of systolic HF patients ($n=988$), digoxin use was associated with non-significant reduction in the combined end points (HR = 0.86, 95% CI = 0.70–1.06, $p = 0.158$) and HF hospitalization (HR = 0.81, 95% CI 0.65–1.01, $p = 0.059$). These associations were similar to those observed in diastolic HF ($n=988$) in the DIG ancillary trial (Table 2).⁶

Discussion

Findings from the present analysis demonstrate that digoxin use was associated with a significant reduction in HF hospitalization during the first 2 years of follow-up and a near-significant reduction at the study end in both systolic and diastolic HF patients. These findings are important as patients with diastolic HF are as likely as systolic HF patients to be hospitalized and yet there are few evidence-based recommendations for these patients. Moreover, nearly half of all HF patients have diastolic HF and this number is expected to increase in the coming decades with the aging of the population.¹

There were 2 distinct differences between systolic and diastolic HF patients in the DIG trial. The sample size of patients with diastolic HF was approximately 7 times smaller (988 versus 6800) and despite their older age, they had better survival profiles than systolic HF patients. Treatment effect is generally more pronounced in subgroups of patients with higher burden of disease severity and poorer outcomes.¹⁸ However, when we examined the effect of digoxin in a random subset of 988 systolic HF patients, who had different baseline characteristics than those with diastolic HF (Figure 1, pre-match), we found similar results suggesting that the lack of a significant effect of digoxin in diastolic HF in the DIG trial was more likely a function of sample size, and is less likely due to differences in baseline patient characteristics between systolic and diastolic HF patients.

Our finding of a similar effect of digoxin in systolic and diastolic HF patients is mechanistically plausible. The neurohormonal activation is a common pathophysiological pathway in both systolic and diastolic HF that may contribute to disease progression. Growing evidence points to neurohormonal antagonism as a more probable mechanism of action of digoxin in HF than its cardiac positive inotropic effect. Digitalis has been shown to reduce the activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system by inhibiting the sodium-potassium adenosine triphosphatase enzyme respectively in vagal afferent fibers and

the kidneys.¹ The beneficial effect of digoxin lost statistical significance after the first 2 years of follow up, and more importantly, the effect of digoxin was not harmful in later years. This diminished late effect may be due to cross-over in later years and the use of higher doses of digoxin in the DIG trial, as evidenced from later post-hoc analyses, which may have resulted in higher cumulative digoxin serum concentrations in later years and elimination of earlier benefits.^{11,19} Low-dose digoxin is a strong independent predictor of low serum digoxin concentrations, which have been shown to reduce mortality.¹¹

Evidence on the treatment of diastolic HF remains scarce. The effect of candesartan on HF hospitalization in diastolic HF was very similar to the effect of digoxin in the ancillary DIG trial.^{7,9} However, digoxin has fewer side effects and is less expensive, an important consideration for patients in the developing nations.⁷ Perindopril was among the few other drugs tested in diastolic HF and it had no effect on the primary outcome of all-cause death or unplanned HF hospitalization.²⁰ Currently, irbesartan and aldosterone are being studied in diastolic HF in 2 separate large randomized clinical trials.^{21,22}

A key limitation of the current analysis is the use of smaller sample size of systolic HF that resulted in non-significant effect of digoxin on the combined end point. However, the magnitude of the effect was similar to that observed in the main trial. Yet, findings from the current analysis demonstrate that digoxin may be effective in reducing HF hospitalization in both systolic and diastolic HF. These findings are relevant to contemporary diastolic HF patients as since the DIG trial no new drug has been shown to be effective in these patients. Digoxin in low dosages should be used in systolic HF patients with or without atrial fibrillation who remain symptomatic despite therapy with ACE inhibitors or angiotensin receptor blockers, and approved beta-blockers, especially in those who cannot afford or tolerate these drugs. In patients with diastolic HF, digoxin should be prescribed to reduce symptoms and hospitalizations. Digoxin may also be helpful in controlling heart rate for those with atrial fibrillation which is more prevalent in diastolic HF.²³

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Figure 1.

Absolute standardized differences before and after propensity score matching comparing covariate values for patients with systolic (ejection fraction $\leq 45\%$) and diastolic (ejection fraction $>45\%$) heart failure

(ACE=angiotensin-converting enzyme; NYHA=New York Heart Association; PS=potassium sparing)

Figure 2a

Figure 2b

Figure 2. Kaplan-Meier plots for (a) combined end point of heart failure (HF) hospitalization or HF mortality, and (b) HF hospitalization alone in systolic (SHF) and diastolic (DHF) heart failure patients receiving digoxin or placebo

Table 1

N (%) or mean (±SD)	Left ventricular ejection fraction			
	≤45% (N=916)		>45% (N=916)	
	Placebo (N=450)	Digoxin (N=466)	P Value	
Age (years)	67 (10)	67 (11)	0.561	
Left ventricular ejection fraction (%)	32 (8)	31 (8)	0.390	
Serum creatinine (mg/dL)	1.3 (0.4)	1.3 (0.4)	0.859	
Estimated glomerular filtration rate (ml/min per 1.73 m ²)	62 (20)	61.5 (19)	0.580	
Duration of heart failure (months)	28 (32)	25 (30)	0.156	
Age ≥65 years	292 (65%)	287 (62%)	0.300	
Female	161 (36%)	154 (33%)	0.384	
Nonwhite	74 (16%)	63 (14%)	0.215	
Estimated glomerular filtration rate <60 ml/min per 1.73 m ²	214 (48%)	238 (51%)	0.287	
Cardiothoracic ratio >0.5	218 (48%)	240 (52%)	0.355	
New York Heart Association functional class				
I	82 (18%)	72 (16%)	0.225	
II	276 (61%)	273 (59%)		
III	87 (19%)	115 (25%)		
IV	5 (1%)	6 (1%)		
Signs or symptoms of heart failure*				
0	3 (1%)	9 (2%)	0.413	
1	17 (4%)	12 (3%)		
2	38 (8%)	40 (9%)		
3	38 (8%)	42 (9%)		
≥4	354 (79%)	363 (78%)		
Previous myocardial infarction	231 (51%)	248 (53%)	0.568	
Current angina pectoris	126 (28%)	140 (30%)	0.496	
Diabetes mellitus	142 (32%)	135 (29%)	0.394	
Hypertension	254 (56%)	284 (61%)	0.167	
Previous digoxin use	162 (36%)	163 (35%)	0.747	

* The clinical signs or symptoms studied included râles, dyspnea at rest or on exertion, orthopnea, limitation of activity, S3 gallop, and radiological evidence of pulmonary congestion.

Table 2
Effect of digoxin on outcomes at the study end in systolic & diastolic heart failure (HF) patients

Outcomes	Original data (N=7788) with 6800 SHF and 988 DHF patients				
	Placebo (n=3403)	Digoxin (n=3397)	Absolute rate difference (%)	Hazard ratio (95% CI)	P value
Systolic HF*					
HF hospitalization or HF mortality	1291 (38%)	1041 (31%)	- 7.3	0.75 (0.69-0.82)	<0.001
HF hospitalization	1180 (35%)	910 (27%)	- 7.9	0.72 (0.66-0.79)	<0.001
Diastolic HF†					
	Placebo (n=496)	Digoxin (n=492)	Absolute rate difference (%)	Hazard ratio (95% CI)	P value
HF hospitalization or HF mortality	119 (24%)	102 (21%)	- 3.3	0.82 (0.63-1.07)	0.136
HF hospitalization	108 (22%)	89 (18%)	- 3.7	0.79 (0.59-1.04)	0.094
	Matched data (N=1832) with 916 SHF and 916 DHF patients				
Systolic HF					
	Placebo (n=450)	Digoxin (n=466)	Absolute rate difference (%)	Hazard ratio (95% CI)	P value
HF hospitalization or HF mortality	143 (32%)	132 (28%)	- 3.5	0.85 (0.67-1.08)	0.188
HF hospitalization	131 (29%)	113 (24%)	- 4.9	0.80 (0.62-1.03)	0.079
Diastolic HF					
	Placebo (n=460)	Digoxin (n=456)	Absolute rate difference (%)	Hazard ratio (95% CI)	P value
HF hospitalization or HF mortality	113 (25%)	93 (20%)	- 4.2	0.79 (0.60-1.03)	0.085
HF hospitalization	102 (22%)	82 (18%)	- 4.2	0.77 (0.57-1.03)	0.074

* Adapted from: The Digitalis Investigation Group Investigators. N Engl J Med 1997;336:525-533.

† Adapted from: Ahmed A, et al. Circulation 2006; 114(5):397-403.

Table 3
Effect of digoxin on outcomes at the end of 2 years in systolic & diastolic heart failure (HF) patients

Original data (N=7788) with 6800 SHF and 988 DHF patients					
Outcomes	Placebo (n=3403)	Digoxin (n=3397)	Absolute rate difference (%)	Hazard ratio (95% CI)	P value
Systolic HF*					
HF hospitalization or HF mortality	999 (29%)	735 (22%)	- 7.8	0.69 (0.63-0.76)	<0.001
HF hospitalization	920 (27%)	667 (20%)	- 7.4	0.68 (0.62-0.75)	<0.001
Diastolic HF†					
HF hospitalization or HF mortality	90 (18%)	67 (14%)	- 4.5	0.71 (0.52-0.98)	0.034
HF hospitalization	86 (17%)	59 (12%)	- 5.3	0.66 (0.47-0.91)	0.012
Matched data (N=1832) with 916 SHF and 916 DHF patients					
Systolic HF					
HF hospitalization or HF mortality	114 (25%)	89 (19%)	- 6.2	0.72 (0.55-0.95)	0.022
HF hospitalization	102 (23%)	80 (17%)	- 5.5	0.73 (0.54-0.97)	0.033
Diastolic HF					
HF hospitalization or HF mortality	86 (19%)	62 (14%)	- 5.1	0.69 (0.50-0.95)	0.025
HF hospitalization	82 (18%)	55 (12%)	- 5.6	0.64 (0.45-0.90)	0.010

* Adapted from: GlaxoSmithKline. Lanoxin (digoxin) tablets, USP: Full prescribing information. 2001.

† Adapted from: Ahmed A, et al. Circulation 2006; 114(5):397-403.