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

Philippe Meyer, MD[a], Michel White, MD[a], Marjan Mujib, MBBS[b], Anna Nozza, MSc[a], Thomas E. Love, PhD[d], Inmaculada Aban, PhD[b], James B. Young, MD[e], William H. Wehrmacher, MD[f], and Ali Ahmed, MD, MPH[b,c,*]

In the Digitalis Investigation Group trial, digoxin-associated decrease 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 could be explained by differences in baseline characteristics and sample size, we used propensity score matching to assemble a cohort of 916 pairs of patients with systolic and diastolic HF who were balanced in all measured baseline covariates. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of the effect of digoxin on outcomes separately in systolic and diastolic HF, at 2 years (protocol prespecified), and at the end of 3.2 years of median follow-up. HF hospitalization or HF mortality occurred in 28% and 32% of patients with systolic HF (HR digoxin vs placebo 0.85, 95% CI 0.67 to 1.08, p = 0.188) and 20% and 25% in those with diastolic HF (HR 0.79, 95% CI 0.60 to 1.03, p = 0.085) receiving digoxin and placebo, respectively. At 2 years, HRs for this combined end point were similar for systolic HF (0.72, 95% CI 0.55 to 0.95, p = 0.022) and diastolic HF (0.69, 95% CI 0.50 to 0.95, p = 0.025). Digoxin also decreased 2-year HF hospitalization in systolic HF (HR 0.73, 95% CI 0.54 to 0.97, p = 0.033) and diastolic HF (HR 0.64, 95% CI 0.45 to 0.90, p = 0.010). In conclusion, as in patients with systolic HF, digoxin was equally effective in those with diastolic HF, who constitute half of all patients with HF, yet have few evidence-based therapeutic options. Published by Elsevier Inc. (Am J Cardiol 2008;102: 1681–1686)

With >1 million hospitalizations each year, heart failure (HF) is the number 1 reason for hospital admission in patients ≥65 years of age in the United States.[1] Nearly ½ of the 5 million patients with HF have diastolic HF and these patients are as likely as those with systolic HF to be hospitalized for HF.[2,3] HF hospitalization is associated with increased mortality, and risk of postdischarge mortality is similar in systolic and diastolic HF.[4] Yet, few interventions to decrease HF hospitalization have been tested in diastolic HF. In the Digitalis Investigation Group (DIG) trial, digoxin significantly decreased HF hospitalization for systolic HF (left ventricular ejection fraction [LVEF] ≤45%) in the main trial (n = 6,800) but not for 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 of the DIG ancillary trial and potential baseline differences between patients with systolic HF and those with diastolic HF.[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 patients with systolic and diastolic HF in equal samples.

Methods

We used a public-use copy of the DIG dataset obtained from the National Heart, Lung, and Blood Institute (NHLBI). The rationale, design, and results of the DIG trial have been previously reported.[5] Briefly, 7,788 patients with chronic HF in normal sinus rhythm were randomized to receive digoxin or placebo. These patients were recruited from 302 clinical centers in the United States (186) and Canada (116) from 1991 to 1993. Patients with an LVEF ≤45% (n = 6,800) were enrolled in the main trial and those with an 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 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 the US Food and Drug Administration approval of digoxin. Because this combined end point was primarily driven by a decrease in HF hospitalization, we also examined that outcome separately. We analyzed the effect of digoxin on these outcomes at study end and at 2 years of follow-up. The 2-year analysis was prespecified in the DIG

[a]Montreal Heart Institute, Montreal, Quebec, Canada; [b]University of Alabama at Birmingham, and [c]VA Medical Center, Birmingham, Alabama; [d]Case Western Reserve University, and [e]Cleveland Clinic Foundation, Cleveland, Ohio; and [f]Loyola University, Chicago, Illinois. Manuscript received April 6, 2008; revised manuscript received and accepted May 20, 2008.

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*Corresponding author: Tel: 205-934-9632; fax: 205-975-7099.

E-mail address: aahmed@uab.edu (A. Ahmed).

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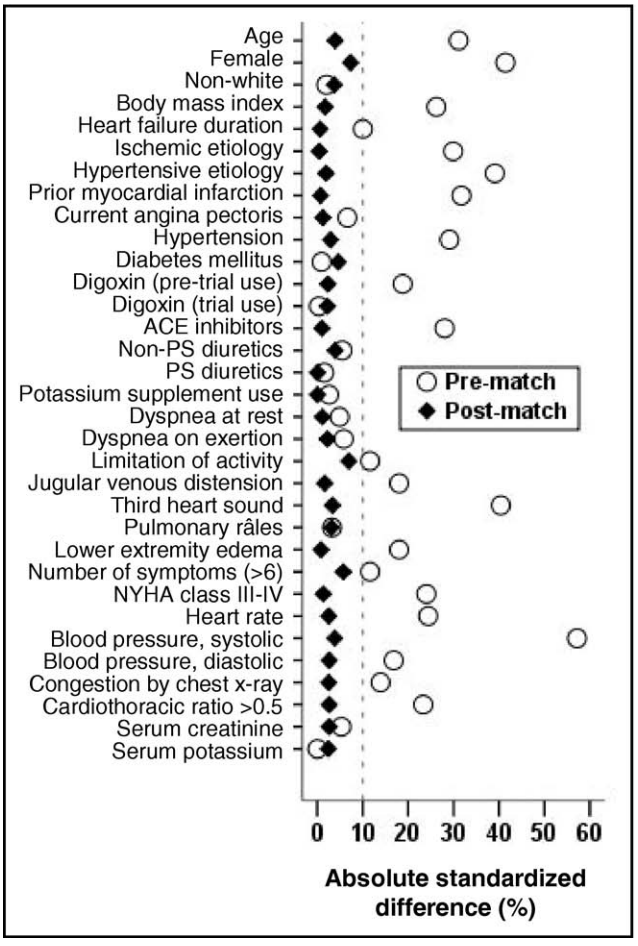

Figure 1. Absolute standardized differences before and after propensity score matching comparing covariate values for patients with systolic HF (LVEF ≤45%) and diastolic HF (LVEF >45%). ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; PS = potassium-sparing.

protocol and was also the basis of Food and Drug Administration approval.[10,11] Outcomes data were classified by DIG investigators who were blinded to patients' study drug assignments and were 98.9% complete.[12]

To ensure that the effect of digoxin in patients with systolic and diastolic HF would not be due in part to differences in baseline characteristics between these 2 groups, we assembled a propensity-matched population in which 916 pairs of patients with systolic and diastolic HF were balanced in all measured baseline covariates. We calculated propensity scores for diastolic HF for each patient using a nonparsimonious multivariable logistic regression model adjusting for all measured baseline covariates displayed in Figure 1.[13,14] Absolute standardized differences <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 the 2 outcomes. To determine if the effect of digoxin persisted despite baseline differences, we repeated our analyses in a cohort of 988 patients with systolic HF randomly selected from the 6,800 patients in the main trial. All analyses were performed on an intention-to-treat basis, with 2-sided p values <0.05 considered statistically significant, using SPSS 15 for Windows (SPSS, Inc., Chicago, Illinois).

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 patients with systolic and diastolic HF are listed in Table 1.

The effect of digoxin on the combined end point of HF hospitalization or HF mortality was similar in patients with systolic HF (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.67 to 1.08, p = 0.188) and those with diastolic HF (HR 0.79, 95% CI 0.60 to 1.03, p = 0.085; Table 2 and Figure 2). There was no significant interaction between digoxin and LVEF, regardless of whether it was used as a categorical (using a 45% cutoff, p = 0.655) or a continuous (p = 0.991) variable. The effect of digoxin on HF hospitalization was also similar in systolic HF (HR 0.80, 95% CI 0.62 to 1.03, p = 0.079) and diastolic HF (HR 0.77, 95% CI 0.57 to 1.03, p = 0.074; Table 2 and Figure 2), also without any interaction.

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

In a random subset of patients with systolic HF (n = 988), digoxin use was associated with a nonsignificant decrease in the combined end points (HR 0.86, 95% CI 0.70 to 1.06, p = 0.158) and HF hospitalization (HR 0.81, 95% CI 0.65 to 1.01, p = 0.059). These associations were similar to those observed in patients with 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 decrease in HF hospitalization during the first 2 years of follow-up and a near-significant decrease at the study end in patients with systolic and diastolic HF. These findings are important because patients with diastolic HF are as likely as those with systolic HF to be hospitalized and yet there are few evidence-based recommendations for these patients. Moreover, nearly ½ of all patients with HF have diastolic HF and this number is expected to increase in the coming decades with aging of the population.[1]

There were 2 distinct differences between patients with systolic HF and those with diastolic HF in the DIG trial. The sample of patients with diastolic HF was approximately 7 times smaller (988 vs 6,800) and, despite their older age, they had better survival profiles than patients with systolic HF. Treatment effect is generally more pronounced in sub-

Table 1
Baseline patient characteristics of propensity-matched patients with systolic and diastolic heart failure, by treatment group

	LVEF ≤45% (n = 916)			LVEF >45% (n = 916)		
	Placebo (n = 450)	Digoxin (n = 466)	p Value	Placebo (n = 460)	Digoxin (n = 456)	p Value
Age (yrs)	67 ± 10	67 ± 11	0.561	67 ± 10	66 ± 11	0.607
LVEF (%)	32 ± 8	31 ± 8	0.390	55 ± 8	55 ± 8	0.744
Serum creatinine (mg/dl)	1.3 ± 0.4	1.3 ± 0.4	0.859	1.27 ± 0.39	1.24 ± 0.39	0.367
Estimated glomerular filtration rate (ml/min/1.73 m^2)	62 ± 20	61.5 ± 19	0.580	61.4 ± 20	63.4 ± 21	0.138
Duration of HF (mos)	28 ± 32	25 ± 30	0.156	28 ± 37	25 ± 30	0.107
Age ≥65 yrs	292 (65%)	287 (62%)	0.300	293 (64%)	280 (61%)	0.474
Women	161 (36%)	154 (33%)	0.384	173 (38%)	174 (38%)	0.864
Nonwhite	74 (16%)	63 (14%)	0.215	59 (13%)	66 (15%)	0.468
Estimated glomerular filtration rate <60 ml/min/1.73 m^2	214 (48%)	238 (51%)	0.287	229 (50%)	207 (45%)	0.184
Cardiothoracic ratio >0.5	218 (48%)	240 (52%)	0.355	234 (51%)	236 (52%)	0.789
New York Heart Association functional class						
I	82 (18%)	72 (16%)	0.225	96 (21%)	84 (18%)	0.405
II	276 (61%)	273 (59%)		255 (55%)	273 (60%)	
III	87 (19%)	115 (25%)		101 (22%)	95 (21%)	
IV	5 (1%)	6 (1%)		8 (2%)	4 (1%)	
Signs or symptoms of HF*						
0	3 (1%)	9 (2%)	0.413	4 (1%)	3 (1%)	0.401
1	17 (4%)	12 (3%)		10 (2%)	6 (1%)	
2	38 (8%)	40 (9%)		31 (7%)	33 (7%)	
3	38 (8%)	42 (9%)		51 (11%)	36 (8%)	
≥4	354 (79%)	363 (78%)		364 (79%)	378 (83%)	
Previous myocardial infarction	231 (51%)	248 (53%)	0.568	241 (52%)	241 (53%)	0.889
Current angina pectoris	126 (28%)	140 (30%)	0.496	131 (29%)	140 (31%)	0.461
Diabetes mellitus	142 (32%)	135 (29%)	0.394	133 (29%)	125 (27%)	0.614
Hypertension	254 (56%)	284 (61%)	0.167	252 (55%)	273 (60%)	0.120
Previous digoxin use	162 (36%)	163 (35%)	0.747	175 (38%)	160 (35%)	0.353
Primary cause of HF						
Ischemic	265 (59%)	283 (61%)	0.876	272 (59%)	274 (60%)	0.932
Nonischemic	185 (41%)	183 (39%)		188 (41%)	182 (40%)	
Hypertensive	98 (22%)	86 (19%)		86 (19%)	91 (20%)	
Idiopathic	48 (11%)	51 (11%)		53 (12%)	51 (11%)	
Concomitant medications						
Nonpotassium-sparing diuretics	357 (79%)	355 (76%)	0.252	357 (78%)	340 (75%)	0.280
Potassium-sparing diuretics	39 (9%)	34 (7%)	0.444	39 (9%)	34 (8%)	0.568
Angiotensin-converting enzyme inhibitors	402 (89%)	401 (86%)	0.131	403 (88%)	397 (87%)	0.803
Nitrates	195 (43%)	196 (42%)	0.697	182 (40%)	188 (41%)	0.608
Daily dose of study medication (mg)						
0.125	82 (18%)	97 (21%)	0.695	103 (23%)	99 (22%)	0.277
0.250	310 (69%)	311 (67%)		315 (69%)	303 (67%)	
0.375	51 (11%)	51 (11%)		34 (7%)	50 (11%)	
0.500	6 (1%)	4 (1%)		5 (1%)	3 (1%)	

Values are means ± SDs or numbers of patients (percentages).

* Clinical signs or symptoms studied included rales, increased jugular venous pressure, peripheral edema, dyspnea at rest or on exertion, orthopnea, limitation of activity, S_3 gallop, and radiologic evidence of pulmonary congestion.

groups of patients with a greater burden of disease severity and poorer outcomes.[17] However, when we examined the effect of digoxin in a random subset of 988 patients with systolic HF who had different baseline characteristics from those with diastolic HF (Figure 1), 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 less likely due to differences in baseline patient characteristics between patients with systolic HF and those with diastolic HF.

Our finding of a similar effect of digoxin in patients with systolic and diastolic HF is mechanistically plausible. The neurohormonal activation is a common pathophysiologic pathway in systolic and diastolic HF that may contribute to

Table 2
Effect of digoxin on outcomes at study end in patients with systolic and diastolic heart failure

Outcomes	Placebo	Digoxin	Absolute Rate Difference (%)	HR (95% CI)	p Value
Original data (n = 7,788) from patients with systolic HF (n= 6,800) and diastolic HF (n = 988)					
Systolic HF*					
No. of patients	3,403	3,397			
HF hospitalization or HF mortality	1,291 (38%)	1,041 (31%)	−7.3	0.75 (0.69–0.82)	<0.001
HF hospitalization	1,180 (35%)	910 (27%)	−7.9	0.72 (0.66–0.79)	<0.001
Diastolic HF†					
No. of patients	496	492			
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 = 1,832) from patients with systolic HF (n = 916) and diastolic HF (n = 916)					
Systolic HF					
No. of patients	450	466			
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					
No. of patients	460	456			
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.[5]
† Adapted from Ahmed et al.[6]

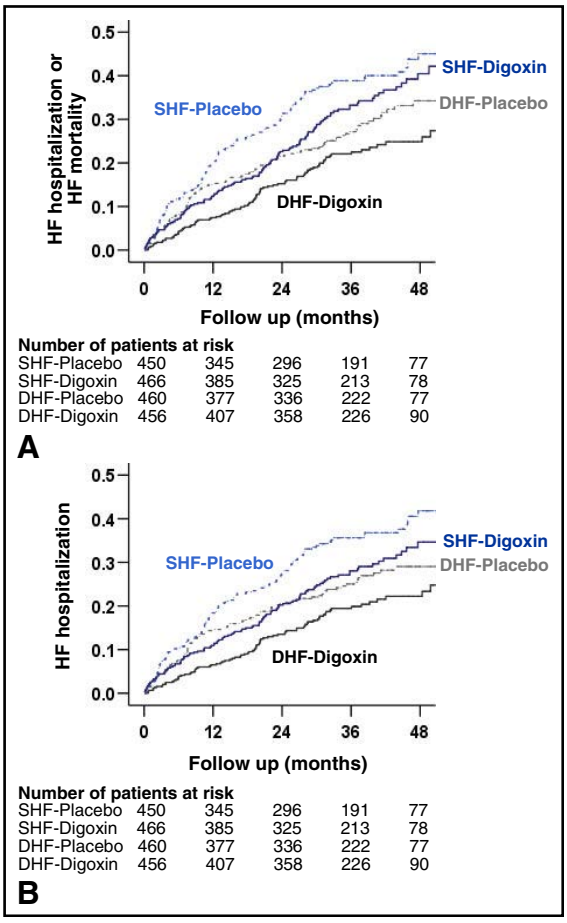

Figure 2. Kaplan-Meier plots for *(A)* combined end point of HF hospitalization or HF mortality and *(B)* HF hospitalization alone in patients with systolic HF (SHF) and those with diastolic HF (DHF) receiving digoxin or placebo.

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 decrease the activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system by inhibiting the sodium-potassium adenosine triphosphatase enzyme in vagal afferent fibers and the kidneys, respectively.[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 decreased late effect may be due to crossover 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 previous benefits.[11,18] Low-dose digoxin is a strong independent predictor of low serum digoxin concentrations, which have been shown to decrease 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 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.[19] Currently, irbesartan and aldosterone are being studied in diastolic HF in 2 separate large randomized clinical trials.[20,21]

A key limitation of the present analysis is the use of a smaller sample of patients with systolic HF that resulted in a nonsignificant 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 present analysis demonstrate that digoxin may be effective

Table 3
Effect of digoxin on outcomes at the end of two years in patients with systolic and diastolic heart failure

Outcomes	Placebo	Digoxin	Absolute Rate Difference (%)	HR (95% CI)	p Value
Original data (n = 7,788) from patients with systolic HF (n = 6,800) and diastolic HF (n = 988)					
Systolic HF*					
No. of patients	3,403	3,397			
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†					
No. of patients	496	492			
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 = 1,832) from patients with systolic HF (n = 916) and diastolic HF (n = 916)					
Systolic HF					
No. of patients	450	466			
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					
No. of patients	460	456			
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, Research Triangle Park, North Carolina. Lanoxin (digoxin) tablets. In: United States Pharmacopeia, 2001.
† Adapted from Ahmed et al.[6]

in decreasing HF hospitalization in systolic and diastolic HF. These findings are relevant to contemporary patients with diastolic HF because, since the DIG trial, no new drug has been shown to be effective in these patients. Digoxin in low dosages should be used in patients with systolic HF with or without atrial fibrillation who remain symptomatic despite therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and approved β blockers, especially in those who cannot afford or tolerate these drugs. In patients with diastolic HF, digoxin should be prescribed to decrease symptoms and hospitalizations. Digoxin may also be helpful in controlling heart rate for those with atrial fibrillation, which is more prevalent in diastolic HF.[22]

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