Effect of digoxin on mortality and hospitalization in patients with congestive heart failure in sinus rhythm: subgroup analysis of the DIG trial

Introduction

Digoxin remains the oldest cardiac medication still utilized in modern medical practice. It was approved for heart failure (HR) in 1998 based on its clinical benefits on reduced HR-specific hospitalizations and mortality found in PROVED, RADIANCE, and DIG clinical trials and has since been commonly prescribed to patients with symptomatic heart failure.[1-3] However, the evidence supporting the beneficial effects of digoxin has been challenged from different aspects, mainly due to concerns over the uncontrolled digoxin withdrawal rate, medication history of digoxin treatment, and the absence of washout periods. As a result, debate surrounding the use of digoxin in treating patients with heart failure persists.[4]

Another factor directly related to drug effects is the serum drug concentration (SDC), which is determined by initiation and titration of digoxin dose, often based on patient's age, gender, renal function, and use of concomitant drugs. Most heart failure patients achieve a SDC of 0.5 to 1.0 ng/mL with doses of 0.125 to 0.250 mg/d, with a significant inverse relationship between the risk for all-cause mortality and SDC, but no added symptomatic, hemodynamic, or neurohormonal benefit was found in higher digoxin doses achieving SDCs above 1.0 ng/ml.[5-6] Other variables associated with prognosis were also found associated with beneficial effects of digoxin where high-risk patients (e.g. NYHA functional class III or IV symptoms, left ventricular EFs <25%, cardiothoracic ratios >55%) experienced significant reduce in all-cause/HF-specific mortality and hospitalization.[7] This suggested that the effects of digoxin could be different and possibly achieve greater significance among certain patients.

With the above-mentioned perspectives, this project aims to explore the relationship between digoxin and mortality and hospitalization using the DIG trial database and further test the hypothesis that the long-term beneficial effects of digoxin are mediated by race, disease severity, previous digoxin use, and study dose prescribed.

Methods

Description of the DIG dataset

The Digitalis Investigation Group (DIG) trial was a randomized, double-blind, multicenter pivotal clinical trial designed to demonstrate the safety and efficacy of Digoxin in congestive heart failure (CHF) patients. The main DIG trial was conducted from 1991 to 1995 and enrolled 6800 patients from 302 clinical centers in the United States and Canada. Patients who had congestive heart failure and a left ventricular ejection fraction of 0.45 or less were eligible for the study regardless of whether the patient had use digoxin in the past. All patients were randomly assigned to receive either digoxin or placebo and attended follow-up visits at the 4th week, 16th week, and every 4 months afterward.

The DIG dataset consists of longitudinal data in patient's baseline characteristics, medical history, changes in clinical and functional status, concomitant medications, survival and hospitalization status, and adverse events collected throughout the main DIG trial.

Measures of the outcomes and effect modifiers

The primary outcomes evaluated in this project were all-cause mortality, hospitalization due to worsening heart failure (WHF), and hospitalization for cardiovascular causes. Cause of death categories included worsening heart failure, other cardiac, other vascular, unknown, and noncardiac, nonvascular cause. First hospitalizations caused by worsening heart failure, arrythmia, digoxin toxicity, myocardial infarction, unstable angina, stroke, coronary revascularization, cardiac transplantation, or other cardiovascular were all considered hospitalization from cardiovascular disease (CVD). The numbers of days from randomization till date of death and the first WHF/CVD hospitalization were used for time-to-event analysis to compare the survival distribution and hazard ratio between digoxin and placebo groups.

Potential effect modifiers race, number of clinical signs or symptoms of CHF, previous us of digoxin, and initial dose of study drug digoxin were used in the secondary analysis to observe any differences of the digoxin effect in each stratum, in other words, whether digoxin provided different clinical benefits on different subgroups. Drug effect modified by race was examined between white and nonwhite patients. Number of symptoms of CHF were divided into three groups: 0-2, 3, and over 4, as greater numbers suggested higher severity of the disease and potentially worse prognosis. Effect modified by previous digoxin use compared patients who took digoxin within one week prior to randomization and those who did not. The initial dose of digoxin prescribed included daily dose of 0.125 mg, 0.250 mg, 0.375 mg, and 0.500mg, which were grouped into 0.125 mg, 0.250 mg, and over 0.375 mg due to the small amount of frequency.

Statistical analysis

Tables of descriptive statistics illustrating patients' demographics and medical history were constructed, and two-sample t-test and chi-square test were used to evaluate difference in subject baseline characteristics between treatment and placebo groups (statistical significance was not expected due to the randomized design of the trial).

Primary analyses included log rank test and Cox proportional-hazards model to test the null hypothesis of no difference in survival distribution, 1) all-cause mortality and 2) hospitalization due to WHF, and 3) hospitalization for CVD causes, between treatment and placebo groups. Proportional hazard assumption for Cox proportional-hazards model was graphically checked by log-log survival plots for constant hazard ratio between treatment and placebo groups over time. Kaplan–Meier method was used to estimate the survival curve.

Secondary analyses used stratified log rank test and cox proportional-hazards model to test the potential effect modifications on survival and to calculate the hazard ratio associated with the event and the 95 percent confidence interval. Interaction terms were included in separate cox models to test the significance of effect modifications.

P-values presented are two-sided and are considered significant at the 0.05 level. All statistical analyses were carried out using SAS version 9.4.

Results

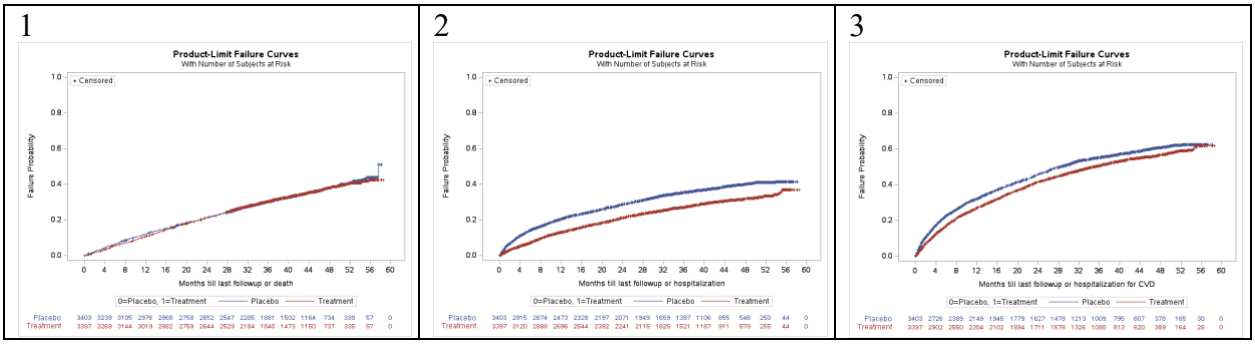
The study population included 6800 patients, with 3397 patients assigned to receiving study drug digoxin and 3403 patients assigned to receiving placebo. Baseline characteristics were balanced between the two treatment groups.

All-cause mortality

There were 1181 deaths in the digoxin group (34.8%) and 1194 deaths in the placebo group (35.1%). No significant difference on all-cause mortality was found between digoxin and placebo groups (HR 0.99; 95% CI 0.91–1.07; P = 0.8013; *Fig. 1 and Table 1*).

Digoxin did not reduce the risk of all-cause death in any of the subgroups, and no interaction was found between the treatments and race, number of clinical signs of CHF, previous us of digoxin, or initial dose of study drug digoxin, indicating that the effect of digoxin was the same among all subgroups.

Figure 1 Kaplan-Meier plots for 1) all-cause mortality, 2) WHF hospitalization, and 3) CVD hospitalization by treatment groups in patients with chronic heart failure in the DIG trial



Hospitalization due to worsening heart failure

The numbers of first hospitalization due to WHF were 910 in the digoxin group (26.8%) and 1180 in the placebo group (34.7%), where digoxin was found to significantly reduce the risk of WHF hospitalization (HR 0.72; 95% CI 0.66–0.79; P < 0.0001; *Fig. 1 and Table 1*).

Protective effects on WHF hospitalization were also observed in most subgroups, expect for patients with 3 clinical signs or symptoms of CHF and patients who started the study drug at 0.125 mg *(Table 2)*. Although no interactions were significant to suggest different effects of digoxin for different race, different numbers of clinical signs of CHF, previous use of digoxin, or different initial doses prescribed, results showed that digoxin had a greater effect on reducing risk of WHF hospitalization for patients who had less than 2 clinical signs or symptoms of CHF compared to those with over 4 signs or symptoms (HR, 0.56 vs. 0.72; P-value for interaction between treatment and signs or symptoms of CHF = 0.0552) *(Table 2)*.

Moreover, there was a trend toward a smaller effect on reducing risk of WHF hospitalization as the daily dose of study drug prescribed increased from 0.125 mg to 0.250 mg and to over 0.350 mg, with hazard ratio of 0.82, 0.71, and 0.61, respectively (P-value for interaction between treatment and initial dose = 0.2066) *(Table 2)*.

Hospitalization for cardiovascular causes

After accounting for all the forementioned cardiovascular causes, there was 4.5 percent more hospitalizations in the digoxin group (1694, 49.9%) than in the placebo group (1850, 54.4%). Hazard ratio between digoxin and placebo groups was greater compared to WHF hospitalization but still indicated a significant association with reduction in CVD hospitalization (HR 0.87; 95% CI 0.81–0.93; P < 0.0001; *Fig. 1 and Table 1*).

Similarly to the results for WHF hospitalization, the effect of digoxin on CVD hospitalization was not modified by any of the pre-selected covariates – race, number of clinical signs of CHF, previous us of digoxin, and initial dose of study drug digoxin *(Table 2)*. The protective effects against CVD hospitalization were more pronounced with less numbers of signs or symptoms of CHF or a stronger daily dose of the study drug. However, among the three categories for numbers of signs or symptoms of CHF, the effect was only significant in patients with 4 or more signs or symptoms of CHF (HR 0.87; 95% CI 0.81–0.94; *Table 2*).

Table 1 Mortality and hospitalization in all vs. subgroups of more severe heart failure patients

	events (%)		Hazard ratio (95% CI)	P-value
Outcome	**Digoxin**	**Placebo**		
All patients	(n = 3397)	(n = 3403)		
All-cause mortality	1181 (34.8)	1194 (35.1)	0.99 (0.91–1.07)	0.8013
CVD hospitalization	1694 (49.9)	1850 (54.4)	0.87 (0.81–0.93)	<0.0001
WHF hospitalization	910 (26.8)	1180 (34.7)	0.72 (0.66–0.79)	<0.0001
4+ signs or symptoms of CHF	(n = 2723)	(n = 2763)		
All-cause mortality	970 (35.6)	954 (34.5)	1.03 (0.95–1.13)	0.4679
CVD hospitalization	1372 (50.4)	1508 (54.6)	0.87 (0.81–0.94)	0.0003
WHF hospitalization	735 (27.0)	960 (34.7)	0.72 (0.66–0.80)	<0.0001
Initial dose at 0.250 mg/day	(n = 2399)	(n = 2384)		
All-cause mortality	844 (35.2)	846 (35.5)	0.99 (0.90–1.09)	0.8458
CVD hospitalization	1187 (49.5)	1288 (54.0)	0.87 (0.80–0.94)	0.0004
WHF hospitalization	641 (26.7)	831(34.9)	0.71 (0.64–0.79)	<0.0001
Initial dose at 0.350+ mg/day	(n = 386)	(n = 415)		
All-cause mortality	142 (36.8)	139 (33.5)	1.12 (0.88–1.41)	0.3520
CVD hospitalization	189 (49.0)	234 (56.4)	0.80 (0.66–0.97)	0.0225
WHF hospitalization	89 (23.1)	141 (34.0)	0.61 (0.47–0.79)	0.0002

Hospitalization in more severe heart failure patients

Digoxin significantly reduced the risk of WHF and CVD hospitalization in three subgroups of patients: 4 or more signs or symptoms of CHF, 0.250 mg initial daily dose, and 350 mg and above initial daily dose of study drug digoxin, which were considered patients with more severe heart failure and worse prognosis *(Table 1)*.

Hazard ratios for WHF and CVD hospitalization in subgroups with >= 4 CHF signs or symptoms, 0.250 mg initial daily dose were almost identical with that in all patients, whereas in patients with >= 0.350 mg initial daily dose, digoxin reduced more WHF and CVD hospitalization *(Table 1)*.

Discussion

The results of this project found no significant difference in all-cause mortality between patients receiving digoxin and those on placebo in all pre-specified subgroups. Other than mortality, digoxin significantly improved hospitalization due to worsening heart failure and

cardiovascular causes. However, the beneficial effects were not uniform across all subgroups, with differences observed based on the number of heart failure symptoms, previous use of digoxin, and the initial dose of study drug prescribed. Despite that none of the pre-specified covariates were effect modifiers, digoxin appeared to be more effective in reducing more hospitalizations when CHF symptoms reduced from 4, if no previous use of digoxin, and when initial dose of study drug increased from 0.250 to 0.350 mg/day *(Table 2)*. It was intriguing that patients who did not use digoxin within one week prior to randomization experienced greater beneficial effects of digoxin, whereas those prescribed a higher initial dose of digoxin showed less benefit.

While digoxin showed consistent efficacy in reducing WHF hospitalizations across racial groups, there was a notable difference in the reduction of cardiovascular disease (CVD) hospitalizations, with a 13% greater risk reduction observed in non-white patients compared to white patients. This discrepancy hints at underlying disparities in cardiovascular risk among different racial populations with CHF.

Table 2 Effect of digoxin on hospitalization for worsening heart failure vs. cardiovascular cause

	WHF hospitalization		CVD hospitalization	
Covariate	**Hazard ratio (95% CI)**	**P-value***	**Hazard ratio (95% CI)**	**P-value***
All patients	0.72 (0.66–0.79)	<0.0001	0.87 (0.81–0.93)	<0.0001
Race		0.9928		0.1009
White	0.72 (0.66–0.79)		0.89 (0.83–0.95)	
Non-white	0.72 (0.59–0.88)		0.76 (0.64–0.90)	
Number of CHF signs or symptoms		0.0552		0.8463
0-2	0.56 (0.42–0.74)		0.82 (0.66–1.01)	
3	0.92 (0.69–1.23)		0.86 (0.69–1.07)	
4+	0.72 (0.66–0.80)		0.87 (0.81–0.94)	
Previous use of digoxin		0.4453		0.4919
Yes	0.74 (0.66–0.84)		0.88 (0.81–0.97)	
No	0.69 (0.61–0.79)		0.85 (0.77–0.93)	
Initial daily dose of study drug		0.2066		0.5611
0.125 mg	0.82 (0.67–1.00)		0.92 (0.78–1.07)	
0.250 mg	0.71 (0.64–0.79)		0.87 (0.80–0.94)	
0.350 mg+	0.61 (0.47–0.79)		0.80 (0.66–0.97)	

*p-value for tests on interaction between Treatment Groups and Covariates

One of the limitations of this project was the study population in DIG trial consisting of predominantly younger white males which differed largely from the contemporary heart failure population. The limited generalizability of the DIG trial has been questioned by many studies[4,7,8] and raises the issue of the equity among different age, sex, and race to receive healthcare resources as needed. Whether certain populations were more susceptible to participating in clinical trials at the time of the DIG trial needs further examination.

It was also notable that higher dose and SDC targets were used in the DIG trial,[7] with the mean SDC of 0.86 ng/ml at the 1-month visit and 0.80 ng/ml at the 12-month visit,[4] while contemporary guideline suggested that an SDC <1.0 ng/ml was enough to achieve favorable effects of digoxin.[4] A study based on post-hoc analysis of the DIG trial also revealed that lower doses of digoxin likely to achieve low SDC (0.9 ng/ml) reduced mortality and hospitalization in patients with CHF.[8] As a result, exploring the relationship between the initial dose of study drug prescribed and the final SDC reached can provide more information on whether the initial dose of digoxin attenuates its effect on mortality and hospitalization.

Lastly, while proportional hazard assumption violations were noted in some Cox models, indicating potential time-dependent effects of digoxin, further exploration of these dynamics was not undertaken in this project. A study investigated the short-term effects of digoxin in high-risk patients and found significant associations with 2-year HF mortality/hospitalization in all patients and all-cause mortality/hospitalization in patients with low SDC.[7] Future research directions could focus on investigating the short-term and long-term effects of digoxin in specific patient subgroups to elucidate its time-dependent efficacy in chronic heart failure management.

In summary, this project analyzed data from the DIG trial to assess the impact of digoxin on mortality and hospitalizations among heart failure patients. While no significant difference in all-cause mortality was detected between patients receiving digoxin and those on placebo, digoxin significantly reduced hospitalizations due to worsening heart failure and cardiovascular causes. Subgroup analysis revealed nuanced effects of digoxin, with variations in efficacy based on factors such as the number of heart failure symptoms, previous digoxin use, and initial drug dose. Notably, disparities in cardiovascular risk reduction between racial groups were observed, suggesting potential differences in treatment response.

References

1. 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(4):955-962.
2. 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.
3. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure: the Digitalis Investigation Group. N Engl J Med. 1997;336(8):525-533.
4. Ambrosy AP, Butler J, Ahmed A, et al. The use of digoxin in patients with worsening chronic heart failure: reconsidering an old drug to reduce hospital admissions. *J Am Coll Cardiol*. 2014;63(18):1823-1832.
5. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation*. 2006;113(21):2556-2564.
6. Adams KF Jr, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol*. 2005;46(3):497-504.
7. Gheorghiade M, Patel K, Filippatos G, et al. 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(5):551-559.
8. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J*. 2006;27(2):178-186.