Clinical Investigations

Potential Effects of Digoxin on Long-Term Renal and Clinical Outcomes in Chronic Heart Failure

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ABSTRACT

Background: Digitalis glycosides are known to improve the hemodynamic and neurohormonal perturbations that contribute to heart failure (HF)−induced renal dysfunction (RD). The objective of this study was to determine if randomization to digoxin is associated with improvement in renal function (IRF) and to evaluate if patients with digoxin-induced IRF have improved clinical outcomes.

Methods and Results: Patients in the Digitalis Investigation Group (DIG) dataset with protocol-driven 1-year serum creatinine levels (performed in a central laboratory; n = 980) were studied. IRF was defined as a postrandomization ≥20% increase in estimated glomerular filtration rate (eGFR). IRF occurred in 15.5% of the population (mean improvement in eGFR 34.5 ± 15.4%) and was more common in patients randomized to digoxin (adjusted odds ratio 1.6; $P = .02$). In patients without IRF, digoxin was not associated with reduced death or hospitalization (adjusted hazard ratio [HR] 0.96, 95% CI 0.8−1.2; $P = .67$). However, in the group with IRF, digoxin was associated with substantially improved hospitalization-free survival (adjusted HR 0.49, 95% CI 0.3−0.8; $P = .006$; P interaction = .026).

Conclusions: In this subset of the DIG trial, digoxin was associated with long-term improvement in kidney function and, in patients demonstrating this favorable renal response, reduction in death or hospitalization. Additional research is necessary to confirm these hypothesis-generating findings. (*J Cardiac Fail 2013;19:295−302*)

Key Words: Cardiorenal syndrome, improved renal function, digoxin, mortality.

Renal dysfunction (RD) has emerged as one of the most powerful risk factors for adverse outcomes in heart failure (HF) and is often a limiting factor in the utilization of evidence-based therapies and maintenance of euvolemia.[1] Notably, static RD, a worsening in renal function, and even an improvement in renal function (IRF) have been associated with worsened survival.[2−5] The high prevalence and prognostic importance of RD in HF has triggered substantial interest in the development of therapeutic strategies aimed at improving renal and clinical outcomes in these patients. Unfortunately, therapeutic agents with direct beneficial effects on renal function, such as the adenosine antagonists, synthetic natriuretic peptides, and vasopressin antagonists, have not meaningfully improved renal or clinical end points in relatively unselected HF populations.[6−8]

Some of the primary drivers of HF-induced RD are the hemodynamic and neurohormonal perturbations typical of severe HF, factors which also directly contribute to adverse outcomes. As such, it is possible that targeting cardiorenal dysfunction upstream from the kidneys (ie, improving the hemodynamics and neurohormonal activation thought to be causing the RD) could provide benefit to these

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high-risk patients for both renal and clinical outcomes. Digitalis glycosides are known to have beneficial hemodynamic and neurohormonal effects in patients with HF.[9] As a result, we hypothesized that HF patients randomized to digoxin would likely have a greater incidence of IRF compared with patients assigned to placebo. We additionally hypothesized that IRF in the setting of initiation of digoxin signifies a favorable therapeutic response to cardiac glycosides and, as such, serves to identify a group of patients that may derive a particularly large reduction in adverse clinical events with continued digoxin use. Thus, the primary objective of this proof-of-concept study was to evaluate the effects of digoxin on long-term changes in kidney function and investigate if patients who experience IRF may have an exaggerated clinical benefit from digoxin therapy.

Methods

The Digitalis Investigation Group (DIG) trial was a National Heart, Lung, and Blood Institute (NHLBI)−sponsored randomized, double-blind, placebo-controlled trial of the effect of digoxin on clinical outcomes in patients with chronic HF. Methods and results have been previously published.[10,11] Briefly, 7,798 patients with chronic heart failure were randomized to digoxin or placebo at 302 clinical centers in the United States and Canada. Patients were eligible if they had a diagnosis of HF based on past clinical symptoms, signs, or radiologic evidence of pulmonary congestion. Patients were required to be on a stable dose of diuretic and an angiotensin-converting enzyme inhibitor (if ejection fraction ≤45%) before entry into the trial. Exclusion criteria included atrial fibrillation, hypo- or hyperkalemia, baseline creatinine level >3.0 mg/dL, listing for cardiac transplantation, or recent myocardial infarction/revascularization. A subset of the original study population underwent protocol-driven assessment of laboratory values, such as serum creatinine and digoxin levels, in a central laboratory. Patients with data available to calculate estimated glomerular filtration rate (eGFR), at both baseline and 1-year study visits, were included in the present analyses (n = 980). There was no difference in the rate of randomization to digoxin in this subset compared with patients without these data available (P = .14). Although differences in baseline characteristics of the patients in the present subset were present compared with patients missing these data, the effect of randomization appeared to be relatively preserved across these differences (Supplemental Table 1).

Estimated GFR was calculated with the 4-variable Modified Diet and Renal Disease (MDRD) equation.[12] Although the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has demonstrated a greater accuracy in the estimation of GFR in several populations, that formula has not been well validated in HF populations. Notably, CKD-EPI gives relative estimates of chronic kidney disease prevalence that are discordant (higher) than those found when comparing CKD-EPI and MDRD in populations where the superior accuracy in estimation of GFR was determined (where chronic kidney disease estimates are lower with CKD-EPI than with MDRD).[1] Therefore, the MDRD equation, which has been extensively used in outcomes-based research in HF, was used in the primary analyses. The primary analyses evaluating the interaction between randomization to study drug, IRF, and death or hospitalization were repeated using the CKD-EPI formula to ensure that similar results were obtained. IRF was defined as baseline−to−1 year ≥20% improvement in eGFR to account for the nonlinear relationship between serum creatinine and GFR and to maintain consistency with our previous studies of IRF.[3,5,13] The DIG trial was conducted and supported by the NHLBI in collaboration with the DIG study investigators. This manuscript was prepared using DIG data obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the DIG study or the NHLBI.

Statistical Methods

The 2 primary analyses in this proof-of-concept study focused on: 1) the relative incidence of IRF between patients randomized to digoxin versus placebo; and 2) the relative association between death or hospitalization and randomization to digoxin in strata of patients that did or did not experience IRF. As such, the primary end points were: 1) the association between IRF and randomization to digoxin; and 2) the interaction between IRF, study drug assignment, and subsequent death or hospitalization. Given the limited number of patients with 1-year eGFR available, the combination of death or hospitalization was chosen as the primary end point to maximize power with planned subanalyses for the component end points. Given the previously reported importance of serum digoxin levels on the mortality benefit of digoxin therapy in this population, subanalysis incorporating digoxin levels at 1 year with the use of previously identified clinically relevant levels was also undertaken.[14] Values reported are mean ± SD, median (quartile 1−quartile 4), and percentile. Independent Student t test or the Mann-Whitney U test was used to compare continuous parameters. Pearson chi-square was used to evaluate categoric variables. Proportional hazards modeling was used to evaluate time-to-event associations with death or hospitalization, with time 0 defined as the 1-year study visit (because by definition patients had to survive to that visit for serum creatinine to be determined). Candidate covariates for multivariable modeling were obtained by screening all baseline variables for a univariate association with either IRF (primary analysis 1) or death or hospitalization (primary analysis 2) for a P value of ≤.2. These covariates were removed with the use of backwards elimination (likelihood ratio), and variables with a P value of ≤.2 were retained.[15] Adjusted survival curves for hospitalization or death were plotted for the 4 combinations of groups between patients that did or did not experience IRF and patients receiving placebo or digoxin. The same covariates used in the primary multivariable models were used to produce the adjusted survival curves. Significance was defined as 2-tailed P < .05 for all analyses, except for tests of interaction, where P values of <.1 were considered to be significant. Statistical analysis was performed with IBM SPSS Statistics version 19.0 (IBM Corp, Armonk, New York).

Results

Baseline characteristics and the effect of randomization to digoxin on death or rehospitalization in the DIG trial has been previously reported.[11] Baseline characteristics of the 980 patients in the present analysis and comparison of those with and without IRF at 1 year are presented in Table 1. In total, 152 patients (15.5%) experienced IRF with a mean improvement in eGFR of 34.5 ± 15.4%.

Table 1. Characteristics of the Overall Cohort and Patients With and Without Improvement in Renal Function (IRF)

Characteristic	Overall Cohort (n = 980)	No IRF (n = 828)	Yes IRF (n = 152)	*P* Value	IRF and Placebo (n = 60)	RF and Digoxin (n = 92)	*P* Value
Demographics							
Age (y)	63.4 ± 10.5	63.8 ± 10.2	61.6 ± 11.8	.021*	60.0 ± 12.7	62.7 ± 11.2	.170
White	88.6%	89.3%	84.9%	.118	86.7%	83.7%	.617
Male	78.6%	80.1%	70.4%	.008*	66.7%	72.8%	.416
Medical history							
Hypertension	43.0%	42.6%	44.7%	.630	41.7%	46.7%	.539
Diabetes mellitus	25.4%	25.6%	24.3%	.743	18.3%	28.3%	.163
Angina	26.0%	26.3%	24.3%	.608	21.7%	26.1%	.535
Myocardial infarction	68.4%	68.8%	65.8%	.457	60.0%	69.6%	.224
Physical examination							
Heart rate	76.5 ± 12.6	76.4 ± 12.6	77.4 ± 12.9	.382	77.9 ± 12.7	77.0 ± 13.1	.657
Systolic blood pressure (mm Hg)	126.6 ± 20.2	126.9 ± 20.2	124.8 ± 19.7	.247	123.0 ± 20.1	126.0 ± 19.5	.360
Pulmonary crackles	71.0%	70.9%	71.7%	.838	71.7%	71.7%	.992
S3 gallop	49.4%	49.4%	49.3%	.990	41.7%	54.3%	.126
Edema	50.2%	48.9%	57.2%	.059	61.7%	54.3%	.373
Jugular venous distention	52.2%	51.0%	59.2%	.061	60.0%	58.7%	.873
Medications (baseline)							
Prior digoxin	49.9%	49.8%	50.7%	.838	45.0%	54.3%	.260
ACE inhibitor	96.2%	96.1%	96.7%	.732	96.7%	96.7%	.980
Potassium-sparing diuretic	11.5%	11.1%	13.8%	.337	18.3%	10.9%	.192
Other diuretic	75.7%	75.6%	76.3%	.851	76.7%	76.1%	.935
Nitrates	36.2%	35.5%	40.1%	.276	40.0%	40.2%	.979
Hydralazine	1.0%	1.0%	1.3%	.693	0.0%	2.2%	.250
Laboratory values (baseline)							
eGFR (mL min^{-1} 1.73 m^{-2})	70.0 ± 21.7	71.4 ± 22.3	62.1 ± 15.3	<.001*	63.7 ± 15.9	61.1 ± 15.0	.297
Serum creatinine (mg/dL)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	.001*	1.3 ± 0.3	1.4 ± 0.3	.339
Laboratory values (1 y)							
eGFR (mL min^{-1} 1.73 m^{-2})	68.4 ± 21.2	65.6 ± 19.9	83.3 ± 21.8	<.001*	85.2 ± 22.4	82.0 ± 21.4	.384
Serum creatinine (mg/dL)	1.3 ± 0.4	1.4 ± 0.5	1.0 ± 0.2	<.001*	1.0 ± 0.3	1.1 ± 0.2	.429
Serum digoxin (ng/mL)†	0.8 ± 0.6	0.9 ± 0.6	0.8 ± 0.5	.078	N/A	0.8 ± 0.5	N/A
Serum digoxin level ≤0.08 ng/mL†	54.7%	52.2%	66.7%	.014*	N/A	66.7%	N/A
Change in eGFR (mL min^{-1} 1.73 m^{-2})	1.6 ± 17.5	-5.8 ± 15.2	21.2 ± 10.2	<.001*	21.5 ± 10.7	21.0 ± 9.9	.771
Change in eGFR (%)	0.6 ± 21.9	-7.0 ± 15.9	34.5 ± 15.4	<.001*	34.2 ± 15.4	34.7 ± 15.5	.850
Functional status/imaging							
Ejection fraction (%)	31.6 ± 12.2	31.5 ± 11.9	32.3 ± 13.7	.481	32.5 ± 14.3	32.2 ± 13.4	.887
Preserved ejection fraction (>45%)	11.7%	11.0%	15.8%	.091	20.0%	13.0%	.250
Cardiothoracic ratio	0.51 ± 0.07	0.52 ± 0.07	0.53 ± 0.07	.082	0.53 ± 0.06	0.53 ± 0.07	.806
NYHA functional class	2.1 ± 0.7	2.1 ± 0.7	2.2 ± 0.7	.090	2.3 ± 0.7	2.2 ± 0.7	.157

ACE, angiotensin-converting enzyme; NYHA, New York Heart Association.
Improvement in renal function (IRF) defined as ≥20% improvement in estimated glomerular filtration rate (eGFR) from randomization to 1 year.
*Significant difference.
†Analysis restricted to patients randomized to digoxin.

Among patients with normal baseline renal function (eGFR >90 mL min^{-1} 1.73 m^{-2}) only 2.7% experienced IRF, whereas in those with significant baseline RD (ie, eGFR <60 mL min^{-1} 1.73 m^{-2}), the incidence of IRF was higher (21.5%; Fig. 1). Baseline characteristics were similar between patients that did and did not experience IRF (Table 1). Notable exceptions were a lower baseline eGFR, a lower prevalence of male sex, and a slightly younger age in the IRF group. In the overall sample, randomization to digoxin was associated with a greater incidence of IRF (18% vs 12%; odds ratio [OR] 1.5; $P = .024$). This association remained significant after adjustment for baseline eGFR (OR 1.5; $P = .03$), eGFR at 1 year (OR 1.5; $P = .026$), and baseline characteristics associated with IRF (sex, race, age, cardiothoracic ratio, New York Heart Association functional class, baseline eGFR: OR 1.6; $P = .018$). Among patients that did experience IRF, the relative degree of improvement in eGFR was similar in the digoxin and placebo groups (Table 1). Furthermore, there were no significant differences in baseline characteristics between patients in the placebo and digoxin groups that experienced IRF (Table 1). In patients experiencing IRF, there were no differences in the use of diuretics, angiotensin-converting enzyme inhibitors, nitrates, hydralazine, or potassium supplementation at 1 year between the placebo and digoxin groups ($P \geq .23$ for all comparisons). Notably, in patients experiencing IRF, the rate of discontinuation of angiotensin-converting enzyme inhibitor therapy was small and similar between the placebo group (2 patients) and the digoxin group (3 patients; $P = .67$).

Digoxin Dose, Level, and IRF

There was no significant difference in the dose of study drug, either immediately after randomization ($P = .39$) or at 1 year ($P = .53$), between those with and those without

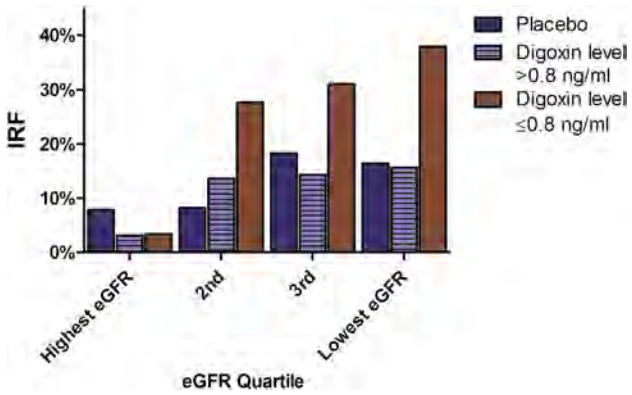

Fig. 1. Incidence of improvement in renal function (IRF) from baseline to 1 year across quartiles of baseline estimated glomerular filtration rate (eGFR). IRF defined as ≥20% improvement in eGFR from randomization to 1 year. Lowest eGFR quartile <57.9 mL min^{-1} 1.73 m^{-2}, third quartile 57.9 mL min^{-1} 1.73 m^{-2} to 70.0 mL min^{-1} 1.73 m^{-2}, second quartile 70.0 mL min^{-1} 1.73 m^{-2} to 83.7 mL min^{-1} 1.73 m^{-2}, highest quartile >83.7 mL min^{-1} 1.73 m^{-2}.

IRF. The same lack of association remained when the analysis was restricted to patients randomized to digoxin (dose immediately after randomization: $P = .33$; dose at 1 year: $P = .60$). In the overall sample, there was a weak inverse relationship between digoxin level at 1 year and IRF (0.78 ± 0.47 ng/mL in IRF vs 0.89 ± 0.54 ng/mL in non-IRF; $P = .046$) that did not persist after controlling for 1-year eGFR ($P = .75$). However, there was a significant interaction between baseline eGFR, digoxin level, and IRF (P interaction = .011) such that among patients with baseline RD (eGFR <60 mL min^{-1} 1.73 m^{-2}) the 1-year digoxin level was substantially lower in the IRF group (0.7 ± 0.4 ng/mL vs 1.1 ± 0.5 ng/mL in those without IRF; $P < .001$; OR for IRF = 0.86 per 0.1 ng/mL increase; $P < .001$). Importantly, this association was unchanged by adjustment for 1-year eGFR (adjusted OR 0.84 per 0.1 ng/mL increase; $P = .008$). The strong relationship between study drug assignment, digoxin level, and the incidence of IRF is depicted in Figure. 1.

Associations With Death or Hospitalization

Over a median follow-up of 1,151 days, a total of 277 patients (28.3%) were hospitalized and 269 (27.4%) died of any cause. The composite end point of death or hospitalization occurred in 418 patients (42.7%). Similarly to the overall trial results, in the subset of patients included in the present analysis, randomization to digoxin did not influence the rate of death (hazard ratio [HR] 0.96, 95% CI 0.75−1.2; $P = .71$). The point estimate for reduction in hospitalization was consistent with that reported in the overall trial (HR 0.85) but did not meet statistical significance in the subset of patients with 1-year creatinine levels available (HR 0.89, 95% CI 0.70−1.1; $P = .31$).[11] Similarly to the previous analysis of the overall population, there was no interaction between baseline eGFR and the rate of death or hospitalization with study drug assignment in this subset (P interaction = .89).[16] Among patients that did not experience IRF, randomization to digoxin was not associated with a reduction in death or hospitalization or with the component end points (Table 2). However, in the group with IRF, randomization to digoxin was associated with a substantial reduction in death or hospitalization (Table 2). Similar results were obtained after substitution of MDRD eGFR with CKD-EPI eGFR for death or hospitalization (P interaction = .02) and the components of death (P interaction = .06) and hospitalization (P interaction = .05).These associations tended to strengthen after controlling for baseline or 1-year eGFR (Table 2). Adjustment for baseline characteristics associated with mortality (age, race, ejection fraction, heart rate, systolic blood pressure, New York Heart Association functional class, diabetes mellitus, baseline use of digoxin, hydralazine, nitrates, diuretics, or angiotensin-converting enzyme inhibitors, physical examination findings, cardiothoracic ratio, and baseline eGFR) minimally altered these associations (Table 2). The reduction in the component end point of death did not meet statistical significance (Table 2), and only with adjustment for baseline eGFR was the reduction in the rate of hospitalization significant in patients with IRF (Table 2). Nonetheless, the point estimates were similar among all end points and the interaction terms remained significant for both death and hospitalization, suggesting that the results noted with the composite end point were unlikely to have been driven by the reduction in hospitalization alone (Table 2). Although limited by power, these results did not appear to differ significantly by baseline eGFR, because the interaction remained significant in those with a baseline eGFR above (adjusted P interaction = .096) or below (adjusted P interaction = .078) the median (3-way P interaction = .48). Notably, in patients with a baseline eGFR below the median (68.9 mL min^{-1} 1.73 m^{-2}), the risk of death or hospitalization associated with randomization to digoxin remained significantly reduced in patients with IRF (adjusted HR 0.49, 95% CI 0.27−0.91; $P = .025$), whereas the group without IRF had no benefit attributable to digoxin (adjusted HR 1.0, 95% CI 0.78−1.4; $P = .78$).

Death or Hospitalization, IRF, and Digoxin Level

Given the previously reported interaction between serum digoxin levels and the effectiveness of digoxin in reducing adverse events, a subanalysis only of patients with a serum digoxin level ≤0.8 ng/mL at 1 year (a threshold previously demonstrated to confer the greatest benefit) was undertaken.[14] Similarly to the findings in the overall sample, in patients with a digoxin level ≤0.8 ng/mL and no IRF the rate of hospitalization, death, or the combined end point was not better with digoxin compared with placebo (Table 3). However, among patients with IRF and a digoxin level ≤0.8 ng/mL at 1 year, the rate of both the combined end point and all-cause mortality were substantially

Table 2. Risk of Death or Hospitalization Associated With Randomization to Digoxin Stratified by Improvement in Renal Function Status

	No IRF		Yes IRF		*P* Value, Interaction
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
Death or hospitalization (n events = 418)					
Unadjusted	0.99 (0.80−1.2)	.910	0.60 (0.37−0.98)	.042*	.066*
Adjusted for baseline eGFR	0.99 (0.80−1.2)	.909	0.56 (0.34−0.92)	.023*	.043*
Adjusted for 12-mo eGFR	1.0 (0.80−1.2)	.995	0.59 (0.33−0.92)	.028*	.029*
Adjusted for baseline characteristics	0.96 (0.77−1.2)	.665	0.49 (0.29−0.81)	.006*	.026*
Death (n events = 269)					
Unadjusted	1.0 (0.81−1.4)	.742	0.59 (0.32−1.1)	.100	.095*
Adjusted for baseline eGFR	1.0 (0.81−1.4)	.752	0.58 (0.31−1.1)	.090	.078*
Adjusted for 12-mo eGFR	1.1 (0.82−1.4)	.636	0.58 (0.31−1.1)	.089	.058*
Adjusted for baseline characteristics	1.0 (0.80−1.3)	.793	0.60 (0.32−1.1)	.120	.064*
Hospitalization (n events = 277)					
Unadjusted	0.96 (0.74−1.2)	.725	0.58 (0.31−1.1)	.082	.149
Adjusted for baseline eGFR	0.96 (0.74−1.2)	.721	0.51 (0.28−0.96)	.035*	.106
Adjusted for 12-mo eGFR	0.97 (0.75−1.2)	.802	0.50 (0.27−0.94)	.030*	.078*
Adjusted for baseline characteristics	0.92 (0.71−1.2)	.523	0.44 (0.23−0.84)	.013*	.053*

Abbreviations as in Table 1. IRF defined as a ≥20% increase in eGFR from randomization to 1 year. Baseline characteristics adjusted for age, race, ejection fraction, heart rate, systolic blood pressure, NHYA functional class, diabetes mellitus, baseline use of digoxin, hydralazine, nitrates, diuretics, or ACE inhibitors, physical examination findings, cardiothoracic ratio, and baseline eGFR.
*Significant difference.

reduced (Table 3; Fig. 2). Unlike mortality, restricting the analysis to patients with a digoxin level ≤0.8 ng/mL at 1 year minimally improved the point estimates for the reduction in hospitalization (Table 3).

IRF and Death or Hospitalization

There was no association between IRF and death or hospitalization in the overall cohort, both before (HR 0.98, 95% CI 0.75−1.3; *P* = .85) and after (HR 1.2, 95% CI 0.93−1.6; *P* = .16) adjustment for eGFR at 1 year (to focus on the change in renal function rather than the absolute eGFR at 1 year). Among patients randomized to digoxin, the lack of association between IRF and death or hospitalization persisted after adjustment for 1-year eGFR (HR 0.96, 95% CI 0.65−1.4; *P* = .83). Despite similar baseline characteristics, in patients randomized to placebo, IRF at 1 year was strongly associated with increased subsequent death or hospitalization (adjusted for 1-year eGFR: HR 1.7, 95% CI 1.2−2.6; *P* = .008; *P* interaction = .029). There were also significant associations between IRF and individual components of death (HR 1.8, 95% CI 1.1−2.9; *P* = .028; *P* interaction = .058) and hospitalization (HR 1.8, 95% CI 1.1−3.0; *P* = .023;

Table 3. Risk of Death or Hospitalization Associated With Randomization to Digoxin Stratified by Improvement in Renal Function Status, in the Subgroup of Patients With 1-Year Serum Digoxin Levels ≤0.8 ng/mL

	No IRF		Yes IRF		*P* Value, Interaction
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
Death or hospitalization (n events = 305)					
Unadjusted	0.86 (0.66−1.1)	.277	0.46 (0.25−0.82)	.010*	.054*
Adjusted for baseline eGFR	0.95 (0.72−1.2)	.676	0.41 (0.24−0.80)	.007*	.023*
Adjusted for 12 month eGFR	0.97 (0.74−1.3)	.827	0.42 (0.23−0.77)	.005*	.014*
Adjusted for baseline characteristics	0.92 (0.70−1.2)	.524	0.30 (0.16−0.58)	<.001*	.018*
Death (n events = 190)					
Unadjusted	0.84 (0.60−1.2)	.316	0.37 (0.16−0.84)	.017*	.066*
Adjusted for baseline eGFR	0.91 (0.65−1.3)	.576	0.36 (0.16−0.82)	.015*	.042*
Adjusted for 12-mo eGFR	0.96 (0.68−1.3)	.807	0.36 (0.16−0.81)	.014*	.029*
Adjusted for baseline characteristics	0.93 (0.66−1.3)	.662	0.35 (0.15−0.79)	.012*	.023*
Hospitalization (n events = 208)					
Unadjusted	0.86 (0.62−1.2)	.354	0.58 (0.29−1.1)	.112	.301
Adjusted for baseline eGFR	0.95 (0.69−1.3)	.755	0.54 (0.28−1.1)	.079	.164
Adjusted for 12-mo eGFR	0.98 (0.71−1.4)	.891	0.52 (0.26−1.0)	.060	.120
Adjusted for baseline characteristics	0.88 (0.64−1.2)	.456	0.38 (0.17−0.82)	.014*	.145

Abbreviations as in Table 1. IRF defined as a ≥20% increase in eGFR from randomization to 1 year. Patients in the placebo group were assumed to have a serum digoxin level of <0.8 ng/mL. Baseline characteristics adjusted for age, race, ejection fraction, heart rate, systolic blood pressure, NHYA functional class, diabetes mellitus, baseline use of digoxin, hydralazine, nitrates, diuretics, or ACE inhibitors, physical examination findings, cardiothoracic ratio, and baseline eGFR.
*Significant difference.

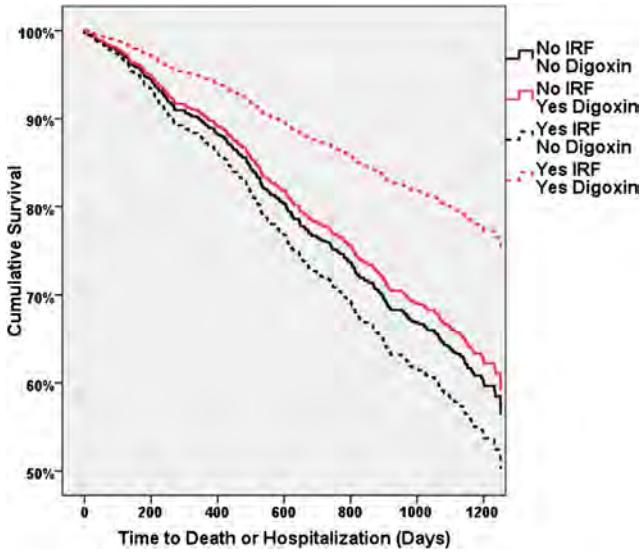

Fig. 2. Adjusted survival curves grouped by randomization to digoxin or placebo and subsequent improved renal function (IRF) status, in patients with a serum digoxin level ≤0.8 ng/mL. IRF defined as ≥20% improvement in estimated glomerular filtration rate (eGFR) from randomization to 1 year. Covariates adjusted for: age, race, ejection fraction, heart rate, systolic blood pressure, New York Heart Association functional class, diabetes, baseline use of digoxin, hydralazine, nitrates, diuretics, or angiotensin-converting enzyme inhibitors, physical examination findings, cardiothoracic ratio, and baseline eGFR. Overall between-group differences: $P = .028$. Comparisons of the Yes IRF/Yes Digoxin (n = 58) and the No IRF/No Digoxin group (n = 409; $P = .007$), No IRF/Yes Digoxin (n = 213; $P = .026$), and Yes IRF/No Digoxin (n = 60; $P = .004$) groups were all statistically significant.

P interaction = .078) in patients in the placebo group. Adjustment for baseline characteristics associated with mortality did not alter the differential association between IRF and death or hospitalization between patients randomized to digoxin or placebo (P interaction = .022).

Discussion

The principal observations of this proof-of-concept study are: 1) Randomization to digoxin appears to be associated with a significantly greater incidence of IRF at 1 year; and 2) digoxin was associated with the greatest reduction in death or hospitalization in the subset of patients that had an improvement in renal function. Among patients with stable renal function from baseline to 1 year, randomization to digoxin or placebo was associated with nearly identical rates of death, hospitalization, or the combination. However, patients assigned to digoxin that had IRF at 1 year (potentially identifying patients that have both baseline cardiorenal dysfunction and physiology responsive to cardiac glycosides), the rate of death or hospitalization was significantly reduced. Importantly, when this analysis was restricted to patients with a serum digoxin level ≤0.8 ng/mL, the association between randomization to digoxin and the reduction in death or hospitalization in patients with IRF strengthened, a finding largely driven by a further reduction in mortality. Although significant limitations inherent to these data exist, these results provide preliminary evidence to suggest that cardiac glycosides may provide benefit for long-term renal and clinical outcomes in selected patients with cardiorenal dysfunction.

With the possible exception of discontinuation of angiotensin-converting enzyme inhibitor therapy (which was rare in this population and similar between groups), there are no commonly used therapeutic maneuvers in HF that can induce IRF independently from a true improvement in the function of the kidney. As such, the finding of IRF strongly suggests that the patient had some degree of baseline cardiorenal dysfunction. Moreover, because the primary defect in most chronic intrinsic kidney disease is an irreversible loss of nephrons, the finding of IRF also helps to distinguish patients with reversible RD from those with chronic intrinsic kidney disease. Given the absence of methodology with which HF-induced RD can be identified, IRF may represent an approach to facilitate identification of patients that will ultimately have improved long term outcomes with cardiorenal therapeutics.

The present findings also support the concept that the factors driving changes in renal function in HF populations may be more important than the actual changes in GFR. Illustrating this, among patients that developed IRF in the present study the magnitude of improvement in eGFR at 1 year was nearly identical between the digoxin and placebo groups. However, there was significantly worsened survival in patients with IRF in the placebo group but no impact on mortality in the digoxin group. Consistent with these findings, we have recently reported that IRF is fairly common in HF, often transient, and associated with significantly worsened survival.[3,5] Given that it is highly unlikely that an improvement in GFR itself would cause poor outcomes, it is probable that IRF identifies a ''sicker'' cohort of patients with limited cardi-renal reserve. Because these patients are ''sicker'' at baseline, it is understandable how this group could have greater rates of adverse clinical outcomes and derive particular clinical benefit from an agent that can provide a sustained improvement in overall hemodynamic and neurohormonal status. Furthermore, it is reasonable to assume that a ''cardiorenal'' intervention with the potential to improve clinical outcomes has a net benefit to the overall cardiorenal axis, which digoxin may provide. A therapeutic intervention that improves renal function but worsens the overall HF (ie, stopping angiotensin-converting enzyme inhibitor or diuretic therapy) would be expected to have an overall net negative effect on clinical outcomes.

Although limited by the small number of observations, the association between a lower serum digoxin level at 1 year and both an increased incidence of IRF and greater net clinical benefit of digoxin in patients that develop IRF have potential mechanistic implications. It is known that digoxin toxicity is linearly related to serum levels and that the positive neurohormonal and hemodynamic effects

are not.[9,17] Notably, the positive neurohormonal effects of digoxin occur at doses where there is minimal effect on contractility or hemodynamics.[18] However, as the dose is increased, hemodynamic improvements occur without significant additional neurohormonal benefit.[19] As the dose is further increased, there actually appears to be an increase in neurohormonal activity.[9] Because digoxin is renally cleared, an argument could be made that the association between IRF and lower 1-year digoxin levels in our study is the result of improved clearance of the drug. However, this association was unchanged after adjustment for the 1-year eGFR, suggesting that improved digoxin clearance is not entirely driving this association. These pharmacodynamic effects of digoxin, in conjunction with the finding that lower serum levels were associated with both a greater incidence of IRF and freedom from death or hospitalization, suggest that the neurohormonal effects could be the predominant mechanism driving the cardiorenal benefits of digoxin in these patients.

Regardless of the mechanism, the fact remains that essentially all of the clinical benefit from digoxin observed in this population was found in the subset of patients that experienced IRF. A possible explanation for this finding is that patients responding to digoxin with IRF had enough baseline cardiorenal dysfunction and pathophysiology responsive to cardiac glycosides to offset the toxicity of this agent. The neutral effect of digoxin in patients without IRF may indicate that those patients did not have a baseline substrate for which the risk-benefit profile of digoxin was favorable. Unfortunately, tailoring therapy based on monitoring for subsequent IRF at 1 year is cumbersome, requires temporary exposure of nonresponders to the risks of therapy, and was in no way tested in this study (ie, discontinuation of digoxin in patients without IRF may worsen outcomes). In light of the above and the limitations inherent to these data, the most direct application of this study is as proof of concept that a high-yield target group exists for digoxin and possibly other cardiorenal therapeutics.

Study Limitations

This study was a post hoc postrandomization subanalysis of a clinical trial with significant missing data, and thus significant potential for confounding exists. As a result, this analysis should be interpreted as hypothesis generating only. The DIG trial was not designed to investigate changes in renal function, and treating physicians were not blinded to measures of renal function obtained for clinical use. As a result, treatment strategies may have been modified in response to these data. Patients with severe renal insufficiency (creatinine >3.0 mg/dL) were excluded from the DIG trial, limiting generalization to this group of patients. Although randomization to digoxin was associated with a greater survival advantage in patients that developed IRF, this finding was the result of a postrandomization subgroup analysis. As a result, causality can not be assumed and it is possible that the associations presented in these studies arose from postrandomization differences in the groups unrelated to study drug assignment. Furthermore, because all patients had to (by definition) be alive at 1 year after randomization to have IRF assessed, significant differences in the patients alive at 1 year compared with those initially randomized at baseline likely exist. Additionally, the lack of ability to determine who is likely to experience IRF with digoxin at baseline is a significant limitation, given that it is impractical to wait a year to evaluate for renal response to determine if the patient is to derive benefit. As a result, it is of particular importance that the findings concerning clinical outcomes be regarded as hypothesis generating only. It is impossible to discern what percentage of the digoxin/IRF group had IRF as a direct result of randomization to digoxin. As a result, there are an unknown percentage of subjects in the digoxin group that likely had spontaneous IRF unrelated to digoxin (much like the placebo group), possibly reducing the effect size. Furthermore, given that patients with IRF on average had lower eGFR at baseline than the remainder of the cohort, regression to the mean likely was responsible for some of the signal for IRF. Although the DIG trial took place before the routine use of therapies such as beta-blockers, aldosterone antagonists, and implantable cardioverter-defibrillators (limiting generalizability to contemporary HF populations), it is exceedingly unlikely that a large randomized trial of digoxin in unselected HF patients will ever be repeated and thus the DIG trial may represent the highest-quality data source ultimately available for this clinical question.

Conclusion

In this subset of the DIG trial, randomization to digoxin was associated with a significantly greater incidence of improvement in kidney function, and the reduction in death or hospitalization attributable to digoxin was primarily derived from the group of patients demonstrating this favorable renal response. These hypothesis-generating results suggest that treatment of patients with baseline cardiorenal dysfunction and physiology responsive to treatment may ultimately provide benefit for long-term renal and clinical outcomes. These positive proof-of-concept findings suggest that future research is warranted to evaluate the role of cardiac glycosides in the treatment of cardiorenal dysfunction and to develop methodology to prospectively identify patients likely to derive benefit from this therapy.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cardfail.2013.03.002.

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