Association of Serum Digoxin Concentration and Outcomes in Patients With Heart Failure

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Context The Digitalis Investigation Group (DIG) trial reported that digoxin provided no overall mortality benefit and only a modest reduction in hospitalizations among patients with heart failure and depressed left ventricular systolic function. The clinical outcomes associated with digoxin therapy at different serum concentrations in the DIG trial have not been assessed.

Objective To assess variations in serum digoxin concentration (SDC) and their association with mortality and hospitalization in patients with heart failure.

Design, Setting, and Patients Post hoc analysis of the randomized, double-blinded, placebo-controlled DIG trial, conducted from August 1991 to December 1995, with the main analysis restricted to men with a left ventricular ejection fraction of 45% or less (n=3782). Patients randomly assigned to receive digoxin were divided into 3 groups based on SDC at 1 month (0.5-0.8 ng/mL, n=572; 0.9-1.1 ng/mL, n=322; and ≥1.2 ng/mL, n=277) and compared with patients randomly assigned to receive placebo (n=2611).

Main Outcome Measure All-cause mortality at a mean follow-up of 37 months.

Results Higher SDCs were associated with increased crude all-cause mortality rates (0.5-0.8 ng/mL, 29.9%; 0.9-1.1 ng/mL, 38.8%; and ≥1.2 ng/mL, 48.0%; *P*=.006 for trend). Patients with SDCs of 0.5 to 0.8 ng/mL had a 6.3% (95% confidence interval [CI], 2.1%-10.5%) lower mortality rate compared with patients receiving placebo. Digoxin was not associated with a reduction in mortality among patients with SDCs of 0.9 to 1.1 ng/mL (2.6% increase; 95% CI, −3.0% to 8.3%), whereas patients with SDCs of 1.2 ng/mL and higher had an 11.8% (95% CI, 5.7%-18.0%) higher absolute mortality rate than patients receiving placebo. The association between SDC and mortality persisted after multivariable adjustment (SDC 0.5-0.8 ng/mL hazard ratio [HR] 0.80, 95% CI, 0.68-0.94; SDC 0.9-1.1 ng/mL HR 0.89, 95% CI, 0.74-1.08; SDC ≥1.2 ng/mL HR 1.16, 95% CI, 0.96-1.39; and HR of 1.00 [referent] for placebo).

Conclusions Our findings demonstrate that higher SDCs were associated with increased mortality and suggest that the effectiveness of digoxin therapy in men with heart failure and a left ventricular ejection fraction of 45% or less may be optimized in the SDC range of 0.5 to 0.8 ng/mL.

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THE DIGITALIS INVESTIGATION Group (DIG) trial, a randomized, double-blinded, placebo-controlled study evaluating the efficacy of digoxin therapy for patients with heart failure, found that digoxin therapy had no effect on mortality but modestly reduced hospitalizations due to worsening heart failure.[1] Patients were randomly assigned to digoxin with the objective of achieving a therapeutic serum digoxin concentration (SDC) in the range of 0.5 to 2.0 ng/mL.[1,2] However, this range was defined to avoid concentrations associated with digoxin toxicity and was not specified as a result of evaluations of the relative efficacy of different SDCs.[3]

Since the publication of the DIG trial, concerns have been raised regarding the relative efficacy of SDCs greater than 1.0 ng/mL. Higher SDCs in this range have been associated with improved left ventricular function[4-6] but have not shown a beneficial effect on neurohormonal function, hemodynamic profile, or exercise tolerance.[4,5,7] Consequently, current clinical practice guidelines of the American College of Cardiology and the American Heart Association state "large doses of digoxin may not be more effective than small

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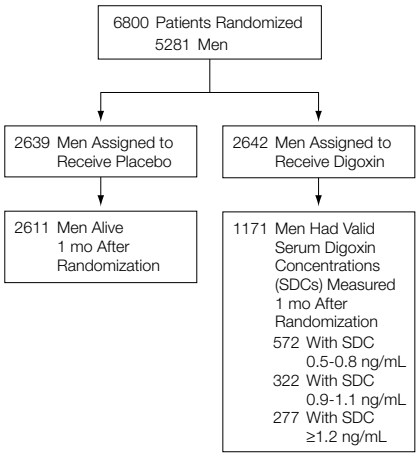
Figure 1. Study Cohort



doses in the treatment of heart failure,"[8] and some textbooks suggest that clinicians pursue target SDCs lower than the upper therapeutic range accepted in the DIG trial.[9,10]

Published evaluations of the efficacy of various SDCs have relied on intermediate end points, such as neurohormonal function or risk of worsening heart failure,[4,5,7] rather than risks of hospitalization or mortality.[4,5,7] Prior studies have not accounted for clinical characteristics, such as age or renal function, that may confound the relationship between SDC and patient outcomes.[11] The 4 published studies of SDC and the efficacy of digoxin therapy have been based on fewer than 210 total patients, drawn from single centers, and evaluated outcomes after digoxin withdrawal, thereby limiting their generalizability to other patient populations and their power to detect differences in efficacy across a range of SDCs.[4-7] Accordingly, we undertook a post hoc evaluation of the DIG trial to evaluate the association of SDC, risk of mortality, and risk of hospitalization among patients with heart failure and left ventricular dysfunction.

METHODS

DIG Trial Database

We obtained a public-use copy of the database of the DIG trial by submitting a written request to the National Heart, Lung, and Blood Institute. None of the authors were members of the DIG Investigators, and thus none were involved in the conduct or initial analysis of the trial.

Study Design

The design and results of the DIG trial have been previously reported.[1,2] The study was conducted from August 1991 to December 1995. Patients with stable, clinically confirmed heart failure, a left ventricular ejection fraction (LVEF) of 45% or less, and were in sinus rhythm were enrolled between August 1991 and February 1993. Patients were randomly assigned to digoxin or placebo based on a published algorithm that accounted for age, sex, weight, and renal function.[12] Modifications in initial dosing were permitted to allow for prior digoxin dosages and concomitant pharmacotherapy.

Study Cohort

Because we have previously identified a sex and digoxin therapy interaction in the DIG trial[13] and only a small number of women had SDCs measured, we restricted our main analysis to men enrolled in the main DIG trial (N=5281) (FIGURE 1). Patients were divided into those randomly assigned to digoxin (n=2642) and those randomly assigned to placebo (n=2639). Serum digoxin concentrations were measured in a random group of men in the digoxin arm 1 month after randomization (n = 1409). We selected patients randomly assigned to digoxin who had valid SDCs assessed at 1 month after randomization with blood samples drawn at least 6 hours after their previous digoxin dose (n=1171). Among the 2639 patients randomly assigned to placebo, we excluded 28 subjects who died in the month following randomization to replicate the same selection process for patients randomly assigned to digoxin. Thus, the study sample consisted of 3782 patients; 2611 randomly assigned to placebo and 1171 randomly assigned to digoxin.

Serum Digoxin Concentration Groups

Patients randomly assigned to digoxin were further divided into 3 groups based on their SDC measured 1 month after randomization using published cut points of clinical interest: 0.5 to 0.8 ng/mL, 0.9 to 1.1 ng/mL, and 1.2 ng/mL and higher.[3,7] No patient in the DIG trial database had a reported SDC that was less than 0.5 ng/mL (TABLE 1).

Outcomes

The primary end point of the DIG trial was all-cause mortality within 37 months (range, 24-48 months) of randomization.[1] We also examined 3 prespecified secondary outcomes in the DIG trial[2]—death due to cardiovascular causes, death due to worsening heart failure, and hospitalization for worsening heart failure—as well as all-cause hospitalization and hospitalization for suspected digoxin toxicity. Causes of death and hospitalization were recorded by local investigators who were blinded to patients' treatment assignments.

Statistical Analysis

Baseline characteristics were compared between patients randomly assigned to placebo and the 3 SDC groups using χ^2 and Wilcoxon rank sum tests. Kaplan-Meier curves were plotted for all-cause mortality for patients in the placebo and the 3 SDC groups. χ^2 Analyses were conducted to compare rates of mortality and hospitalization between patients randomly assigned to placebo and the 3 SDC groups and to test for trends in outcomes across the SDC groups.

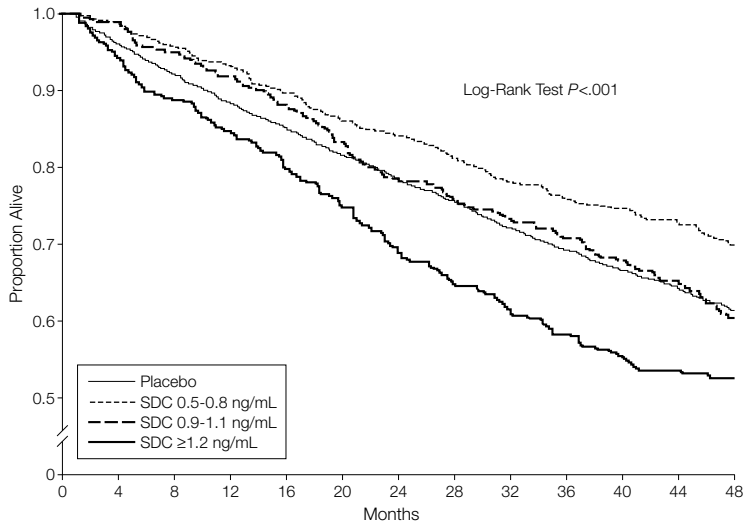
A multivariable Cox proportional hazards analysis was conducted to determine the independent association of SDC and all-cause mortality. Patient characteristics incorporated in our multivariable analysis included age, race, body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), LVEF, New York Heart Association class, cardiothoracic ratio, number of heart failure signs

Table 1. Patient Characteristics*

	All Patients	Placebo Group	Digoxin Group (n = 1171)				
			Serum Digoxin Concentration, ng/mL				
			0.5-0.8	0.9-1.1	≥1.2	*P* for Trend†	*P* Overall‡
No. of patients	3782	2611	572	322	277		
Demographics							
Age, mean (SD), y	63.2 (10.4)	63.2 (10.5)	62.4 (10.7)	63.2 (10.7)	65.6 (9.6)	.008	<.001
Race, black, No. (%)	486 (12.8)	351 (13.4)	65 (11.4)	34 (10.6)	36 (13.0)	.25	.33
Baseline characteristics							
LVEF, mean (SD), %	28.1 (8.7)	28.0 (8.7)	28.7 (8.4)	27.9 (9.1)	27.8 (8.8)	.29	.80
New York Heart Association class, No. (%)							
I	558 (14.8)	374 (14.3)	109 (19.1)	50 (15.5)	25 (9.0)	.38	.001
II	2102 (55.6)	1456 (55.8)	317 (55.4)	176 (54.7)	153 (55.2)	.53	.99
III	1048 (27.7)	733 (28.1)	136 (23.8)	89 (27.6)	90 (32.5)	.48	.052
IV	71 (1.9)	46 (1.8)	10 (1.8)	6 (1.9)	9 (3.2)	.63	.39
No. of heart failure signs or symptoms, No. (%)							
0	49 (1.3)	32 (1.2)	11 (1.9)	1 (0.3)	5 (1.8)	.82	.19
1	86 (2.3)	57 (2.2)	12 (2.1)	13 (4.0)	4 (1.4)	.69	.14
2	295 (7.8)	193 (7.4)	60 (10.5)	27 (8.4)	15 (5.4)	.97	.03
3	363 (9.6)	234 (9.0)	66 (11.5)	36 (11.2)	27 (9.8)	.18	.21
≥4	2989 (79.0)	2095 (80.2)	423 (74.0)	245 (76.1)	226 (81.6)	.25	.003
BMI, mean (SD), kg/m^2	27.2 (4.8)	27.3 (4.8)	27.3 (4.8)	26.6 (4.6)	26.5 (4.8)	<.001	.02
Heart rate, mean (SD), beats/min	78 (13)	78 (13)	77 (13)	77 (13)	78 (12)	.02	.91
Systolic blood pressure, mean (SD), mm Hg	125 (19)	126 (20)	125 (18)	123 (19)	125 (20)	.07	.98
Cardiothoracic ratio, mean (SD), $\times 10^{-2}$	52.4 (6.9)	52.5 (6.9)	51.9 (6.4)	52.2 (7.4)	52.5 (6.8)	.29	.99
Estimated GFR, mean (SD), mL/min	65.0 (21)	65.1 (22)	68.1 (18)	64.7 (19)	57.4 (19)	<.001	<.001
Serum creatinine, mean (SD), mg/dL§	1.33 (0.4)	1.33 (0.4)	1.25 (0.3)	1.32 (0.3)	1.48 (0.4)	<.001	<.001
Medical history							
Duration of heart failure, mean (SD), mo	32 (39)	31 (38)	32 (37)	38 (44)	36 (42)	.002	.06
Prior myocardial infarction, No. (%)	2620 (69.3)	1804 (69.1)	393 (68.7)	231 (71.7)	192 (69.3)	.63	.79
Current angina, No. (%)	979 (25.9)	665 (25.5)	156 (27.3)	78 (24.2)	80 (28.9)	.38	.47
Diabetes, No. (%)	1027 (27.2)	701 (26.8)	153 (26.8)	90 (28.0)	83 (30.0)	.31	.72
Hypertension, No. (%)	1605 (42.4)	1136 (43.5)	219 (38.3)	127 (39.4)	123 (44.4)	.35	.08
Primary cause of heart failure, No. (%)							
Ischemic	2793 (73.8)	1924 (73.7)	421 (73.6)	237 (73.6)	211 (76.2)	.52	.85
Hypertensive	265 (7.0)	196 (7.5)	42 (7.3)	11 (3.4)	16 (5.8)	.03	.04
Idiopathic	493 (13.0)	327 (12.5)	75 (13.1)	52 (16.2)	39 (14.1)	.13	.31
Other	231 (6.1)	164 (6.3)	34 (5.9)	22 (6.8)	11 (4.0)	.31	.45
Medication use, No. (%)							
Prior use of digoxin	1704 (45.1)	1156 (44.3)	262 (45.8)	159 (49.4)	127 (45.8)	.18	.36
Potassium-sparing diuretics	299 (7.9)	213 (8.2)	39 (6.8)	22 (6.8)	25 (9.0)	.81	.55
All other diuretics	2888 (76.4)	2001 (76.7)	402 (70.3)	249 (77.6)	236 (85.2)	.06	<.001
ACE inhibitor	3597 (95.1)	2480 (95.0)	547 (95.6)	307 (95.3)	263 (95.0)	.80	.93
Nitrates	1620 (42.8)	1124 (43.0)	203 (35.5)	143 (44.4)	150 (54.2)	.03	<.001
Hydralazine	67 (1.8)	47 (1.8)	9 (1.6)	5 (1.6)	6 (2.2)	.93	.93
Dosage of study medication prescribed, No. (%)							
0.125 mg/d	504 (13.3)	368 (14.1)	75 (13.1)	34 (10.6)	27 (9.8)	.01	.09
0.250 mg/d	2765 (73.1)	1881 (72.0)	432 (75.5)	231 (71.7)	221 (79.8)	.02	.02
0.375 mg/d	457 (12.1)	326 (12.5)	54 (9.4)	51 (15.8)	26 (9.4)	.48	.02
0.500 mg/d	43 (1.1)	27 (1.0)	10 (1.8)	4 (1.2)	2 (0.7)	.92	.46

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.
*Because of rounding, all percentages may not sum to 100.
†Comparison of trend across the 3 serum digoxin concentration groups.
‡Comparison of patients randomized to placebo and the 3 serum digoxin concentration groups.
§To convert mg/dL to µmol/L, multiply by 88.4.

Figure 2. Kaplan-Meier Survival Analysis for All-Cause Mortality



No. at Risk

Placebo	2611	2514	2405	2302	2213	2117	2024	1948	1858	1625	1385	1111	852
SDC 0.5-0.8 ng/mL	572	566	549	533	512	490	477	459	441	427	419	361	290
SDC 0.9-1.1 ng/mL	322	319	306	295	282	267	250	240	232	225	211	180	138
SDC ≥1.2 ng/mL	277	262	246	234	221	206	187	177	166	159	150	133	116

SDC indicates serum digoxin concentration. The figure presents the cumulative survival rates for patients assigned to placebo and patients assigned to digoxin in the 3 SDC groups over a mean follow-up of 37 months.

and symptoms, systolic blood pressure, heart rate, estimated glomerular filtration rate, duration of heart failure, primary cause of heart failure, history of myocardial infarction, angina, diabetes, hypertension, prior use of digoxin, and use of potassium-sparing diuretics, all other diuretics, angiotensin-converting enzyme inhibitors, nitrates, hydralazine, and other vasodilators.[14] Multivariable analyses were repeated for the end points of death due to cardiovascular causes, death due to worsening heart failure, all-cause hospitalization, and hospitalization due to worsening heart failure.

Analyses were repeated modeling SDCs as a continuous variable with risk-adjusted all-cause mortality rates estimated using fractional polynomial modeling.[15] Secondary analyses also were conducted by excluding patients with an SDC greater than 2.0 ng/mL, which was outside of the DIG trial's prespecified therapeutic range. Although the sample size did not confer adequate power, we also evaluated the association of SDC and all-cause mortality among the 330 women who had valid SDCs evaluated at 1 month and compared their outcomes with the 756 women in the DIG trial randomly assigned to placebo.

The study was approved by the Yale University School of Medicine Human Investigation Committee. All analyses were conducted using SAS 8.02 statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Study Sample

Of the 1171 men with SDCs assessed at 1 month following randomization, 572 (49%) patients had an SDC of 0.5 to 0.8 ng/mL, 322 (27%) patients had an SDC of 0.9 to 1.1 ng/mL, and 277 (24%) patients had an SDC of 1.2 ng/mL or greater. Patients with higher SDCs were older, had greater numbers of heart failure signs or symptoms, and had lower median BMIs and estimated glomerular filtration rates. A greater proportion of patients with higher SDCs were in New York Heart Association class III/IV and had used non–potassium-sparing diuretics and nitrates. There were no clinically meaningful differences observed in LVEF, primary cause of heart failure, prior use of digoxin, medical history, or digoxin dosages of 0.375 mg/d or higher among patients with different SDCs (Table 1).

Serum Digoxin Concentration and Mortality

There was no difference in all-cause mortality among patients randomly assigned to placebo and patients randomly assigned to digoxin who had SDCs assessed (36.2% placebo vs 36.6% digoxin, $P=.80$). Kaplan-Meier survival curves, however, differed based on patients' SDCs ($P<.001$) (FIGURE 2). Higher SDCs were associated with higher crude all-cause mortality ($P=.006$ for trend) and cardiovascular mortality ($P<.001$ for trend), but not mortality due to worsening heart failure ($P=.68$ for trend) (TABLE 2).

The effectiveness of digoxin therapy compared with placebo varied based on patients' SDCs. Patients with SDCs of 0.5 to 0.8 ng/mL had a 6.3% (95% confidence interval [CI], 2.1%-10.5%) lower rate of all-cause mortality, a 3.7% (95% CI, 0.4%-7.7%) lower rate of cardiovascular mortality, and a 4.7% (95% CI, 2.1%-7.3%) lower rate of mortality due to worsening heart failure compared with patients randomly assigned to placebo. Patients with SDCs of 0.9 to 1.1 ng/mL had similar rates of all-cause mortality, cardiovascular mortality, and mortality due to worsening heart failure as patients randomly assigned to placebo. In contrast, patients with SDCs of 1.2 ng/mL and higher had an 11.8% (95% CI, 5.7%-18.0%) higher all-cause mortality rate and an 11.5% (95% CI, 5.4%-17.5%) higher cardiovascular mortality rate than patients randomly assigned to placebo, but no increased risk of mortality due to worsening heart failure (1.9%, 95% CI -2.6% to 6.3%) (Table 2).

Patients with an SDC of 0.5 to 0.8 ng/mL remained at lower risk of all-cause mortality (hazard ratio [HR], 0.80; 95% CI, 0.68-0.94) and mortality due to worsening heart failure (HR, 0.66; 95%

Table 2. Serum Digoxin Concentration and Mortality and Hospitalization Rates*

	Mortality			Hospitalization		
	All-Cause	Cardiovascular	Worsening Heart Failure	All-Cause	Worsening Heart Failure	Toxicity
Placebo (n = 2611)	36.2 (945)	30.4 (794)	13.3 (347)	67.8 (1769)	34.8 (910)	0.8 (22)
Digoxin overall (n = 1171)	36.6 (429)	32.4 (380)	11.9 (139)	66.8 (782)	25.7 (301)	1.6 (19)
Absolute difference, % (95% CI)†	0.4 (–2.9 to 3.8)	2.0 (–1.2 to 5.2)	–1.4 (–3.7 to 0.8)	–1.0 (–4.2 to 2.3)	–9.2 (–12.2 to –6.0)	0.8 (0.0 to 1.6)
P value‡	.80	.21	.23	.56	<.001	.04
Serum digoxin concentration						
0.5-0.8 ng/mL (n = 572)	29.9 (171)	26.8 (153)	8.6 (149)	61.9 (354)	20.8 (119)	1.2 (7)
Absolute difference, % (95% CI)†	–6.3 (–10.5 to –2.1)	–3.7 (–7.7 to 0.4)	–4.7 (–7.3 to –2.1)	–5.9 (–10.2 to –1.5)	–14.0 (–17.8 to –10.2)	0.4 (–0.6 to 1.4)
P value‡	.005	.09	.002	.007	<.001	.39
0.9-1.1 ng/mL (n = 322)	38.8 (125)	34.5 (111)	14.9 (48)	72.4 (233)	31.1 (100)	0.9 (3)
Absolute difference, % (95% CI)†	2.6 (–3.0 to 8.3)	4.1 (–1.4 to 9.6)	1.6 (–2.5 to 5.7)	4.6 (–0.6 to 9.8)	–3.8 (–9.2 to 1.6)	0.1 (–1.0 to 1.2)
P value‡	.36	.14	.43	.10	.18	.87
≥1.2 ng/mL (n = 277)	48.0 (133)	41.9 (116)	15.2 (42)	70.4 (195)	29.6 (82)	3.2 (9)
Absolute difference, % (95% CI)†	11.8 (5.7 to 18.0)	11.5 (5.4 to 17.5)	1.9 (–2.6 to 6.3)	2.6 (–3.0 to 8.3)	–5.2 (–10.9 to 0.4)	2.4 (0.3 to 4.5)
P value‡	<.001	<.001	.39	.37	.09	<.001
Global *P* value§	<.001	<.001	.007	.006	<.001	.004
P value for trend‖	.006	<.001	.68	.37	<.001	.003

Abbreviation: CI, confidence interval.
*Values are presented as the percentage (No.) of patients experiencing mortality or hospitalization. Values have been rounded.
†Absolute differences are reported as the difference in the percentage of mortality or hospitalization among patients assigned to digoxin (overall, 3 serum digoxin concentration groups [SDCs]) compared with patients assigned to placebo. A negative number indicates a lower rate among patients assigned to digoxin compared with patients assigned to placebo while a positive number indicates a higher rate among patients assigned to digoxin compared with patients assigned to placebo.
‡*P* for the comparison of the rate among patients assigned to digoxin compared with the rate among patients assigned to placebo.
§*P* for the comparison of mortality and hospitalization rates among patients assigned to placebo and the 3 SDC groups.
‖*P* for the comparison of the trend in mortality and hospitalization rates across the 3 SDC groups.

CI, 0.49-0.89) and showed a trend toward a lower risk of cardiovascular mortality (HR, 0.86; 95% CI, 0.72-1.02) after multivariable adjustment. (TABLE 3) In contrast, patients with an SDC of 0.9 to 1.1 ng/mL had mortality risks comparable with those of patients randomly assigned to placebo. Multivariable adjustment attenuated the increased mortality risk among patients with an SDC of 1.2 ng/mL and higher, but a trend toward increased risk of all-cause and cardiovascular mortality persisted.

The association of SDC and all-cause mortality was similar when plotting SDC as a continuous variable (FIGURE 3) and when excluding patients with an SDC greater than 2.0 ng/mL (results not shown).

Serum Digoxin Concentration and Hospitalization

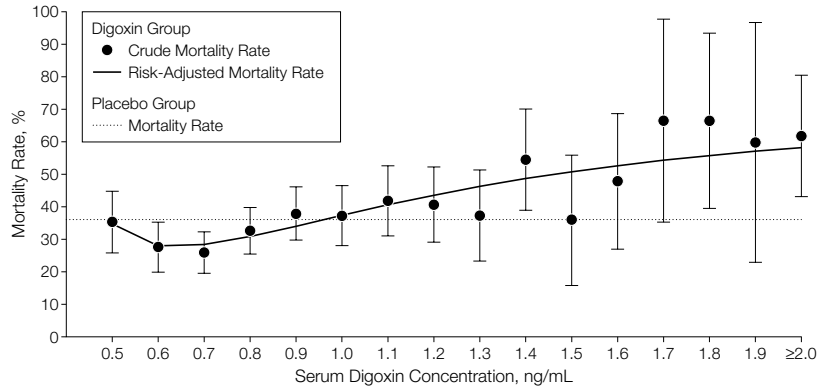
Higher SDCs were associated with higher crude rates of all-cause hospitalization, hospitalization for worsening heart failure, and hospitalization for sus-

Table 3. Serum Digoxin Concentration and Crude and Adjusted Hazard Ratio of Mortality and Hospitalization

		HR (95% CI) by Serum Digoxin Concentration, ng/mL*		
	Placebo	0.5-0.8	0.9-1.1	≥1.2
		Mortality		
All-cause				
Crude	Referent	0.72 (0.61-0.85)	0.99 (0.82-1.19)	1.34 (1.12-1.61)
Adjusted*	Referent	0.80 (0.68-0.94)	0.89 (0.74-1.08)	1.16 (0.96-1.39)
Cardiovascular				
Crude	Referent	0.77 (0.65-0.92)	1.05 (0.86-1.28)	1.40 (1.15-1.70)
Adjusted*	Referent	0.86 (0.72-1.02)	0.93 (0.76-1.14)	1.21 (0.99-1.47)
Worsening heart failure				
Crude	Referent	0.56 (0.41-0.75)	1.03 (0.76-1.39)	1.15 (0.84-1.59)
Adjusted*	Referent	0.66 (0.49-0.89)	0.86 (0.63-1.17)	0.95 (0.69-1.31)
		Hospitalization		
All-cause				
Crude	Referent	0.78 (0.70-0.88)	1.06 (0.93-1.22)	1.02 (0.88-1.18)
Adjusted*	Referent	0.83 (0.74-0.93)	1.02 (0.89-1.18)	0.90 (0.77-1.04)
Worsening heart failure				
Crude	Referent	0.52 (0.43-0.64)	0.83 (0.67-1.02)	0.79 (0.63-0.99)
Adjusted*	Referent	0.56 (0.46-0.67)	0.74 (0.60-0.92)	0.65 (0.52-0.82)

Abbreviations: CI, confidential interval; HR, hazard ratio.
*A multivariable Cox proportional hazards models adjusted for age, race, body mass index, left ventricular ejection fraction, New York Heart Association class, cardiothoracic ratio, number of heart failure signs and symptoms, systolic blood pressure, heart rate, estimated glomerular filtration rate, duration of heart failure, primary cause of heart failure, history of myocardial infarction, angina, diabetes and hypertension, prior use of digoxin, and use of potassium-sparing diuretics, all other diuretics, angiotensin-converting enzyme inhibitors, nitrates, hydralazine, and other vasodilators.

Figure 3. All-Cause Mortality Rates by Serum Digoxin Concentration Groups



The figure presents the crude all-cause mortality rate with 95% confidence intervals and the risk-adjusted rate for patients assigned to digoxin according to their serum digoxin concentration. The mortality rate in patients assigned to placebo is presented for comparison. The risk-adjusted mortality rate was estimated using fractional polynomial modeling.

pected digoxin toxicity (Table 2). Patients with an SDC of 0.5 to 0.8 ng/mL had a 5.9% (95% CI, 1.5%-10.2%) lower crude rate of all-cause hospitalization than patients randomly assigned to placebo. This relationship primarily reflected a 14.0% (95% CI, 10.2%-17.8%) lower absolute rate of hospitalization for worsening heart failure. Patients with an SDC of 0.9 to 1.1 ng/mL and 1.2 ng/mL and higher had all-cause hospitalization rates comparable with patients randomly assigned to placebo. Hospitalization for suspected digoxin toxicity was higher among patients with an SDC of 1.2 ng/mL and higher (2.4%; 95% CI, 0.3%-4.5%) compared with patients randomly assigned to placebo. Rates of hospitalization for suspected digoxin toxicity were comparable with placebo in the other SDC groups (Table 2). Findings were similar after multivariable adjustment, although the higher risk of hospitalization due to worsening heart failure was reduced among patients with SDCs of 0.9 to 1.1 ng/mL and 1.2 ng/mL and higher (Table 3).

Serum Digoxin Concentration and All-Cause Mortality in Women

Of the 330 women who had SDCs measured at 1 month following randomization, 131 (39.6%) had an SDC of 0.5 to 0.8 ng/mL, 96 (29.1%) had an SDC of 0.9 to 1.1 ng/mL, and 103 (31.1%) had an SDC of 1.2 ng/mL and higher. Women also exhibited a pattern of increased all-cause mortality rates at higher SDCs (0.5-0.8 ng/mL, 25.2%; 0.9-1.1 ng/mL, 33.3%; ≥1.2 ng/mL, 41.8%; $P=.009$ for trend). Compared with the 756 women randomly assigned to placebo, higher SDCs continued to be associated with all-cause mortality after multivariable adjustment (0.5-0.8 ng/mL: HR, 0.89; 95% CI, 0.61-1.29; 0.9-1.1 ng/mL: HR, 1.18; 95% CI, 0.81-1.72; and ≥1.2 ng/mL: HR, 1.26; 95% CI, 0.90-1.76), although the findings were not statistically significant.

COMMENT

Our results indicate that the effectiveness of digoxin in the DIG trial varied according to patients' SDCs, such that higher SDCs were associated with higher rates of mortality and hospitalization. Furthermore, our analyses suggest that previously accepted SDCs of 1.2 ng/mL and higher[3,16,17] may be harmful and that currently recommended therapeutic SDCs of approximately 1.0 ng/mL[9,18] may not provide any clinical benefit compared with placebo. Our findings suggest that an SDC of 0.5 to 0.8 ng/mL likely constitutes the optimal therapeutic range for digoxin therapy among men with stable heart failure and left ventricular dysfunction.

Questions concerning the relative efficacy of digoxin therapy as a function of SDC were raised when the DIG trial was first published.[19] The discordance between our findings and previous evaluations of SDCs and patient outcomes[4-7] may be attributable to several factors. Previous attempts to examine the efficacy of SDCs and patient outcomes focused on intermediate outcomes rather than major clinical end points, and thus only examined SDCs in terms of relative efficacy (ie, changes in left ventricular contractility), not possible harm (ie, mortality).[4-7] Furthermore, these studies were likely unable to detect variations in outcomes based on SDCs because they included small numbers of patients observed during brief follow-up periods.[4-7] Prior studies also did not account for the sex and digoxin therapy interaction we identified in a prior evaluation of the DIG trial,[13] indicating earlier findings concerning SDCs may represent an artificial combination of sex-specific variations in digoxin's effect.

The association of SDC and patient outcomes may reflect the dissociated neurohormonal and inotropic effects of digoxin observed at different concentrations.[11,20-22] Neurohormonal modulation is believed to contribute to digoxin's symptomatic benefits among patients with stable heart failure in sinus rhythm.[5,20,22-24] These benefits are achieved at an SDC of 0.7 to 0.8 ng/mL and do not appear to increase at higher SDCs.[3] In contrast, digoxin-associated harms are believed to reflect inotropic-associated increases in myocardial oxygen consumption and arrhythmogenesis at higher serum concentrations.[5,25,26] Thus, our findings are consistent with the hypothesis that digoxin provides a neurohormonal benefit with minimal inotropic-associated risk at lower SDCs.[3,20,21,25,26] As the SDC increases, the inotropic action of digoxin becomes stronger and begins to offset the therapeutic benefits provided by neurohormonal modulation and may account for

the increased risk of mortality at concentrations of 1.2 ng/mL and higher observed in our study and previous evaluations.[27,28] Thus, an SDC of 0.5 to 0.8 ng/mL may represent the most clinically efficacious balance of digoxin's competing neurohormonal and inotropic effects.

Our findings challenge the belief that digoxin is not associated with mortality among patients with heart failure in sinus rhythm and suggest that the neutral association of digoxin and all-cause mortality reported in the main DIG trial publication likely obscured an association between SDC and mortality. Digoxin-associated mortality risks have previously been shown to be dose-dependent in patients recovering from acute myocardial infarction[29] and are similar to serum concentration–dependent mortality risks reported for other positive inotropic agents.[30] Digoxin, however, was associated with mortality reduction at an SDC of 0.5 to 0.8 ng/mL, suggesting that digoxin may offer a survival advantage in a narrow therapeutic window. Because we cannot definitively exclude the possibility of residual confounding, our findings should be considered hypothesis generating. A digoxin-associated mortality reduction may be plausible if the neurohormonal actions of digoxin observed at low serum concentrations were sufficient to reduce the rate of heart failure progression by attenuating neuroendocrine abnormalities associated with increased mortality.[22,31] Trials of other inotropic agents also have shown trends toward a reduction in mortality at low doses, but increased mortality at higher doses.[32,33] Clearly, additional research is needed to confirm these findings and clarify the mechanisms underlying the digoxin-associated mortality effects we observed.

The association of SDC and mortality in women merits particular attention. We previously identified a sex and digoxin therapy interaction such that women randomly assigned to digoxin were at greater risk of all-cause mortality than women randomly assigned to placebo.[13] Although the 131 women with an SDC of 0.5 to 0.8 ng/mL had a mortality risk point estimate below that of women randomly assigned to placebo, our analysis was insufficiently powered to determine whether digoxin use was associated with benefit, harm, or had a neutral effect for women in this or any SDC range. These data are consistent with our prior findings of a digoxin-associated harm in women[13] in that they suggest there is no serum concentration range in which digoxin may provide a benefit to women nor a range in which a digoxin-associated increased mortality risk in women can be definitively excluded.

Our study has certain issues to consider. First, because our study is a post hoc analysis of nonrandomized treatment subgroups in the DIG trial, we cannot exclude the influence of unmeasured factors. However, our analysis accounted for BMI and estimated glomerular filtration rate, 2 of the primary determinants of digoxin absorption and excretion. We used SDCs measured at 1 month after randomization, thus excluding a small group of patients who died in the month following randomization. However, 1 month provided a reasonable time frame in which to ensure serum levels provided an accurate measure of patients' steady state SDCs. Furthermore, SDC levels were generally stable during the course of the DIG trial.[1] Serum digoxin concentrations may not accurately estimate digoxin tissue concentrations given variations in serum level measurement.[34] However, SDCs drawn at least 6 hours after the most recent dose in a cohort with a fixed digoxin dose for 30 days are unlikely to reflect inaccurate serum concentration measurements.

Data concerning the use of β-blockers was not collected as part of the DIG trial, making it unclear whether the overall association of SDC and patient outcomes would be altered by the routine use of β-blockers. A randomized controlled trial that incorporated contemporary management strategies would be necessary to definitively establish the current incremental value of digoxin, and of different digoxin concentrations, in patients with left ventricular systolic dysfunction. In the absence of such a trial, these data provide the best available evidence concerning the relative value of digoxin therapy in the heart failure armamentarium.

Our study is the first, to our knowledge, to examine the association of different SDCs and major clinical end points. Although based on a post hoc analysis of the DIG trial, our results suggest that an SDC of 0.5 to 0.8 ng/mL was associated with lower rates of mortality and hospitalization. Given that no study has demonstrated any substantive clinical benefit for higher SDCs, prudent practice would support an SDC of 0.5 to 0.8 ng/mL as a revised therapeutic range. The feasibility of achieving SDCs within this range in daily clinical practice is unclear. Only a randomized controlled trial can confirm this recommendation; however, we believe our data provide sufficient grounds for consideration of lower target SDCs for men with stable heart failure and left ventricular dysfunction.

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Acquisition of the data: Krumholz.
Analysis and interpretation of the data: Rathore, Curtis, Wang, Bristow, Krumholz.
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Critical revision of the manuscript: Rathore, Curtis, Wang, Bristow, Krumholz.
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Science is the knowledge of many, orderly and methodically digested and arranged, so as to become attainable by one. The knowledge of reasons and their conclusions constitutes *abstract*, that of causes and their effects, and of the laws of nature, *natural science*.
—John Frederick William Herschel (1792-1871)