Clinical Trials

The Effect of Digoxin on the Quality of Life in Patients With Heart Failure

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ABSTRACT

Background: The Digitalis Investigation Group (DIG) trial was a randomized double-blind placebo-controlled study that examined the effect of digoxin on mortality in 7,788 patients with heart failure and sinus rhythm. A prespecified substudy evaluated the effect of digoxin therapy on health-related quality of life (HQOL) in a subset of these patients.

Methods: Patients in the DIG trial had clinical heart failure and were randomized to either digoxin or placebo in addition to their baseline diuretic and angiotensin-converting enzyme therapy (n = 7,788). The patients in this substudy had HQOL measured using a self-administered questionnaire employing scales that measured general health, physical functioning, depression, anger, anxiety, life satisfaction, and disease specific measures. A subjective assessment by the investigator and a 6-minute walk test evaluated functional status. HQOL was measured at baseline and at the 4- and 12-month follow-up visits.

Results: The baseline characteristics of the patients in the quality of life substudy (n = 589) were comparable to the remaining patients in the study (n = 7,199) by age and other clinical measures, including history of prior myocardial infarction or etiology of heart failure; heart failure was of shorter duration and the ejection fraction was slightly better than in the main trial. Within the substudy, patients receiving digoxin (n = 298) or placebo (n = 291) were also similar in baseline characteristics. There was no statistically significant difference in any HQOL measure between the digoxin and the placebo groups at baseline. At the 4-month visit, only perceived health was improved in the digoxin group. At 12 months, there was no statistically significant difference in perceived health, physical functioning, Minnesota Living with Heart Failure, depression, anxiety, anger, Ladder of Life, or the 6-minute walk between the digoxin and placebo groups.

Conclusion: In this subset of the DIG population, digoxin therapy had no effect on the HQOL in patients with heart failure in sinus rhythm.

Key Words: Exercise tolerance, 6-minute walk test, DIG trial.

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Heart failure remains a common disorder, affecting 4.7 million Americans[1]; its frequency is expected to increase as the American population continues to age. Heart failure is associated with depression and a decreased quality of life (QOL).[2,3] Treatment of heart failure with angiotensin-converting enzyme (ACE) inhibitors, agents that can reduce mortality in patients with heart failure, has resulted in only modest[4] or no effect[5,6] on measures of health-related QOL (HQOL). More recently, trial employing β-blockers have demonstrated HQOL benefits and improvements in survival.[7] The large, randomized Digitalis Investigators Group (DIG) trial recently reported that digoxin reduces hospitalizations for worsening heart failure, but has no overall effect on mortality in patients with heart failure.[8] Two smaller randomized trials suggested that patients with heart failure withdrawn from digoxin experienced clinical deterioration,[9,10] whereas one of those trials also noted a worsening of HQOL in patients withdrawn from digoxin.[10] Given the importance of attempting to improve the HQOL in this group of patients and the uncertainty regarding the effectiveness of any agent in improving the HQOL in this setting, we designed a substudy of the DIG trial to examine the effects of digoxin treatment on the HQOL in patients with heart failure. Of secondary interest was the relationship between HQOL indicators and severity of illness and changes in HQOL measures over time.

The DIG trial was a randomized, multicenter, double-blind, placebo-controlled clinical trial that examined the effects of digoxin on mortality in 7,788 patients with clinical heart failure and sinus rhythm. The trial included 6,800 patients with an ejection fraction less than .45 and an additional 988 patients with an ejection fraction of more than .45. The rationale and design of the study and the baseline characteristics of the patients have been reported previously.[11] The study was organized and conducted by a steering committee representing the National Heart, Lung, and Blood Institute; the Department of Veterans Affairs Cooperative Studies Program; and cardiologists from clinical centers in the United States and Canada who participated in the trial. Several substudies were specified in the protocol, including an evaluation of the effects of treatment with digoxin on QOL. Patients eligible to participate in the DIG trial were randomly assigned to digoxin, with a median dose of digoxin .25 mg per day (3,889 patients) or placebo (3,899 patients), in addition to diuretics and ACE inhibitors. The study was approved by the institutional review board at each participating center. All patients provided informed consent.

Methods

Quality of Life

Clinical centers that expressed interest in the QOL substudy enrolled sequential patients into the QOL substudy as they were recruited into the main trial. This QOL substudy included patients with heart failure with ejection fractions above and below .45. Evaluation of HQOL included the assessment of symptoms, physical functioning, and mental health and subjective and objective measurements of functional status[12] as employed in other heart failure trials.[4] In a subsample of 589 (7.6%) of the DIG study patients, HQOL was assessed by a short self-administered QOL questionnaire, and functional status was assessed by a 6-minute walk test at baseline and at the 4- and 12-month follow-up visits. The questionnaire measured four QOL domains (Table 1). First, *perceived health* was assessed using two items taken from the Medical Outcomes Study Short Form 36 (MOS SF-36) measure.[13] Second, *physical functioning*, including performance of basic, intermediate, and vigorous physical activities, was measured using 10 items taken from the MOS SF-36.[13] Third, *life satisfaction* was measured using the Ladder of Life, an item that uses a 1 to 10 scale to assess overall satisfaction with one's life.[14] Fourth, *emotional functioning* was assessed using three scales: depressive symptoms were measured using the short form

Table 1. Health-Related Quality of Life Measures Used in the DIG Study

Measure	Source	Number of Items	Scores for Each Item	Range of Measure	Good Function
Perceived health	MOS SF-36[13]	1	1–5	1–5	High
Physical functioning	MOS SF-36[13]	10	1–3	10–30	High
Disease-specific quality of life	Minnesota Living with Heart Failure[18]	21	0–5	0–105	Low
Depression	CES-Depression Scale[15]	11	0–3	0–33	Low
Anxiety	Spielberger State Anxiety Inventory[16]	10	1–4	10–40	Low
Anger	Spielberger State Anger Inventory[17]	10	1–3	10–40	Low
Life satisfaction	Ladder of Life[14]	1	1–10	1–10	High
Functional status	Six-minute Walk[12]	1	>0 feet		High

DIG, Digitalis Investigation Group; MOS SF-36, Medical Outcomes Study Short Form 36; CES, Centers for Epidemiologic Studies.

(11-item) Centers for Epidemiologic Studies-Depression Scale (CES-D)[15]; anxiety was assessed with the 10-item Spielberger State Anxiety Inventory[16]; and anger was measured with the 10-item Spielberger State Anger Inventory.[17] In addition to these generic QOL measures, the Minnesota Living with Heart Failure questionnaire[18] was used as a disease-specific measure of quality of life. Functional status was measured using the 6-minute walk test[12] in which patients are asked to walk as far as they can in 6 minutes, resting whenever necessary. The investigator also subjectively assessed each patient's functional status using the New York Heart Association (NYHA) functional class. Approximately 20 minutes were required to complete the questionnaire.

The QOL measures used in the DIG trial have been reported to be both reliable and valid for heart failure patients.[19] The multiple-item measures (i.e., all measures except for the Ladder of Life) have been found to have a high degree of internal consistency; Cronbach's alpha coefficients ranged from 0.78 for the CES-D Scale to 0.93 for Speilberger's State Anger Scale,[19] with values greater than 0.75 being considered reliable.

Statistical Methods

Median, 25th, and 75th percentiles for each HQOL measurement are given for baseline, 4-, and 12-month measurements. Means, standard deviations, and proportions are given for demographic variables. The Kruskal-Wallis test[20] is used to compare the HQOL questionnaire measurements at 4 and 12 months between the digitalis group and the placebo group. A *t*-test is used to compare the 6-minute walk measurements at 4 and 12 months. Similarly, a Kruskal-Wallis test is used to compare the change from baseline at 4 and 12 months by treatment group assignment for each of the HQOL questionnaire measurements, and a *t*-test is used to compare the change from baseline to 4 and 12 months for the 6-minute walk measurement. Unadjusted *P* values are presented in the article; these comparisons were all prespecified in the protocol.[21] Nonparametric confidence intervals are calculated for the comparisons of digoxin to placebo at 4 and 12 months.[22] All analyses were performed using SAS[23] software.

Linear regression models were used to determine what variables predicted 12-month measurements. Independent variables in the model were baseline HQOL, gender, treatment status, NYHA functional class, ejection fraction, and age. First-order interactions were tested and dropped from the model because of nonsignificance.

Missing Data

Data were considered missing if a participant died, could not or would not fill out the questionnaire, or submitted an incomplete questionnaire. Missing data were not included in the primary analyses but their significance was subsequently assessed with sensitivity analysis. If data are missing randomly between treatment and control groups, simply ignoring missing data would yield valid results. There are many ways to account for missing data.[24] To check the assumption of data being randomly missing, sensitivity analyses were performed by replacing missing values using various assumptions. To minimize the possibility of concluding digoxin had improved HQOL when in fact it did not (a type I error), missing data were substituted with the worst possible ranks for the questionnaire measurements. Sensitivity analyses were also performed assigning best values to both groups—best values to one group and worst values to the other group—and by imputing an intermediate value for both groups. Sensitivity analyses for the 6-minute walk measurements used a Kruskal-Wallis test and replaced missing data with the worst ranks.[24] Baseline characteristics of patients with missing data were compared with those with complete data.

Results

Clinical and demographic baseline characteristics of the HQOL substudy patients were comparable to the remainder of the DIG study patients except for the duration of heart failure and baseline ejection fraction. There was somewhat less use of nitrates and angiotensin-converting enzyme inhibitors in the substudy patients (Table 2).

The DIG trial patients in NYHA functional classes III/IV had worse HQOL scores compared with those in NYHA classes I or II (Table 3), demonstrating that as the severity of disease progressed the HQOL measures did indeed worsen; this would support the construct validity of the measures selected to evaluate HQOL. Patients in HYHA classes III/IV reported worse general health, poorer physical functioning, more depression, worse Minnesota Living with Heart Failure scores, and less distance walked in the 6-minute walk test than those in NYHA functional class I or II ($P < .05$).

Complete responses to the QOL questionnaire were obtained in 90% at the 4-month follow-up patients and 78% in the 12-month follow-up patients. There were no differences between baseline characteristics for those who had missing data and those who did not. The analyses in Table 4 do not include missing data, but sensitivity analyses that assign missing values to the worst scores, best scores, or intermediate scores to treatment and placebo groups yield similar results. If best scores are imputed to one group and worst scores to the other group, HQOL scores do differ significantly between the two groups.

Regression analysis demonstrated that baseline HQOL measures were significant predictors of 12-month measures, but no other relationships were apparent.

Table 2. Baseline Characteristics of the Health-Related Quality of Life Substudy Participants

Characteristics	HQOL Substudy Participants (n = 589)		Remaining DIG Participants (n = 7199)	
	Digoxin (n = 298)	Placebo (n = 291)	Digoxin (n = 3591)	Placebo (n = 3608)
Age, mean ± SD	64.6 ± 11.8	64.6 ± 11.5	63.8 ± 11.0	63.9 ± 10.7
% > 70	31.9	31.3	27.7	28.4
Male (%)	73.8	73.2	75.4	75.4
Nonwhite (%)	14.1	14.1	14.4	14.7
Previous use of DIG (%)	38.3	38.5	43.2	44.0
Previous MI (%)	63.4	65.6	62.8	63.1
Current angina (%)	31.5	27.8	27.2	26.7
Left ventricular ejection fraction, mean ± SD	34.8 ± 13.0	34.5 ± 13.5	31.8 ± 12.4	31.7 ± 12.5*
Duration of CHF, median (mo)	11.5	9.0	18	18*
Primary etiology of CHF				
Ischemic	68.8	66.0	69.2	69.1
Idiopathic	16.1	14.4	14.8	13.7
Hypertension	10.4	14.1	10.0	10.4
Other	4.7	5.5	6.0	6.8
Signs and symptoms of CHF (%)†				
0	1.3	1.0	1.1	1.0
1	2.3	1.4	2.2	2.1
2	4.7	5.5	7.2	7.2
3	9.4	9.3	9.1	8.9
4+	82.2	82.8	80.4	80.8
Concomitant medications (% using)				
Diuretics	79.2	79.0	81.1	82.3
ACE inhibitors	87.3	88.0	93.6	94.1*
Nitrates	38.6	35.4	42.1	43.1*
Other vasodilators	0.67	1.72	1.00	1.44
NYHA status (%)				
I	13.1	13.8	14.5	14.0
II	54.6	53.9	54.0	54.9
III	30.6	29.6	29.4	29.3
IV	1.7	2.7	2.1	1.8
Diabetes (%)	26.5	28.5	28.3	28.8
Hypertension (%)	42.6	47.4	47.5	47.2

*HQOL substudy participants significantly different from the remainder of the DIG substudy patients ($P = .001$).

†Signs and symptoms of heart failure counted were: rales; elevated jugular venous pressure; peripheral edema; dyspnea at rest or orthopnea; dyspnea on exertion; limitation of activity; S3 gallop; radiologic evidence of pulmonary congestion.

HQOL, health-related quality of life; DIG, Digoxin Investigation Group; SD, standard deviation; MI, myocardial infarction; CHF, congestive heart failure; ACE, angiotensin-converting enzyme; NYHA, New York Heart Association.

Table 3. Baseline Health-Related Quality of Life Scores by Functional Class

Measure (Range of Scores)	Source	Baseline New York Heart Association Functional Class*		
		I	II	III/IV
Number of patients		78	315	187
Perceived health (1–5)	MOS SF-36[13]	4 ± 1	3 ± 1	2 ± 1
Physical functioning (10–30)	MOS SF-36[13]	25 ± 4	22 ± 5	17 ± 4
Depression (0–30)	CES-Depression Scale[15]	5 ± 5	9 ± 6	11 ± 6
Disease-specific quality of life (0–105)	Minnesota Living With Heart Failure[18]	20 ± 21	31 ± 21	44 ± 21
Functional status	Six-minute Walk	375 ± 105	339 ± 107	263 ± 123

*Mean ± SD.

Table 4. Summary of DIG Health-Related Quality of Life Substudy Results

Measure	Treatment	Median (25th, 75th Percentiles)			*P* Value: Baseline to	*P* Value: Baseline to	*P* Value (95% CI*): Digoxin *vs.* Placebo	*P* Value (95% CI*): Digoxin *vs.* Placebo
		Baseline	4 Mo	12 Mo	4 Mo	12 Mo	at 4 Mo	at 12 Mo
Perceived health	Digoxin	3.4 (2.0, 3.4)	3.4 (2.0, 3.4)	3.4 (2.0, 4.4)	.0010	.0007	.0057 (0.1, 0.4)	.3713 (–0.1, 0.3)
	Placebo	3.4 (2.0, 3.4)	3.4 (2.0, 3.4)	3.4 (2.0, 3.4)	.2168	.0014		
Physical functioning	Digoxin	20 (17, 25)	21 (17, 25)	21 (17, 26)	.0382	.5503	.9113 (–3, 2)	.9627 (–3, 2)
	Placebo	21 (17, 25)	21 (17, 26)	21 (17, 25)	.4409	.9492		
Disease-specific quality of life	Digoxin	27 (16, 48)	23 (9, 42)	26 (10, 43)	.0001	.0589	.0764 (–9, 1)	.4308 (–7, 3)
	Placebo	32 (18, 52)	26 (13, 49)	27 (12, 46)	.0005	.0249		
Depression	Digoxin	8 (4, 12)	7 (4, 11)	7 (4, 11)	.3206	.3949	.2525 (–4, 1)	.7739 (–3, 2)
	Placebo	8 (5, 14)	7 (4, 13)	7 (4, 11)	.0347	.0170		
Anxiety	Digoxin	15 (11, 19)	14 (10, 20)	14 (10, 19)	.7671	.1710	.3745 (–3, 1)	.2569 (–3, 1)
	Placebo	15 (12, 21)	15 (10, 21)	15 (11, 19)	.0366	.0645		
Anger	Digoxin	10 (10, 10)	10 (10, 10)	10 (10, 10)	.0847	.8302	.5648 (–2, 1)	.8717 (–2, 1)
	Placebo	10 (10, 10)	10 (10, 10)	10 (10, 10)	.9308	.6328		
Life satisfaction	Digoxin	7 (5, 8)	7 (5, 8)	7 (5, 8)	.2921	.5160	.5535 (–0.1, 0.2)	.8646 (–0.2, 0.2)
	Placebo	7 (5, 8)	6 (5, 8)	7 (5, 8)	.6217	.6488		
Functional status (feet walked)†	Digoxin	316.5 (122.6)	334.1 (137.0)	336.3 (131.6)	.0071	.0281	.8010‡ (–19.8, 25.8)	.7764‡ (–27.9, 19.9)
	Placebo	323.1 (115.3)	331.2 (124.8)	339.7 (121.9)	.3552	.9838		

*Confidence intervals including zero indicate no difference between digoxin and placebo. Because of the ties in the data and the fact that we were calculating nonparametric confidence intervals, it was not possible to calculate exact 95% confidence intervals. Therefore, the confidence intervals for physical functioning, disease-specific quality of life, depression, anxiety, and anger are >99% confidence intervals (this is as close to 95% confidence intervals as possible).

†Mean and standard deviation.

‡*P* value is based on the *t*-test.

A little over one third of the patients in this substudy were receiving digoxin before entry into the trial (see Table 2). Half of them were randomized to placebo; therefore, in effect, they were withdrawn from digoxin therapy. We performed Kruksal-Wallis tests looking for any differences in previous digoxin use for the placebo and digoxin groups at the 4-month period on any HQOL measure. For the digoxin treatment group, there were no differences in any measure looking at previous digoxin use. For patients who were assigned placebo, only the disease-specific QOL measure showed a significant difference between the groups with and without previous digoxin therapy (27.2 versus 34.3, respectively; $P = .0055$). For this measure, a lower score indicates better functioning (see Table 1).

The multiple measures of HQOL used in the study did not show any significant changes at 12 months resulting from digoxin therapy (see Table 4); a small improvement in perceived health associated with digoxin therapy was present at 4 months only. The improvement in this measure despite no apparent change in medians was due to a few values in the tails of the distribution that significantly influenced the results. Changes for each HQOL measure were analyzed at 4 and 12 months. There were small improvements compared with baseline in a number of measures, both in the digoxin and placebo groups; some differences persisted over time whereas other disappeared. The distance walked in the 6-minute walk test did improve in the digoxin group. Confidence intervals for the primary comparisons of digoxin versus placebo are included in Table 4, and also show no difference between treatment groups except for the perceived health measure at 4 months.

The number of patients with a baseline functional class assessment (n = 580) (see Table 3) and the total number patients in the QOL substudy (n = 589) differ because of incomplete baseline data in some patients.

No effect of digoxin treatment on HQOL scores was noted when treatment groups were analyzed by severity of heart failure (NYHA functional class I and II patients compared with NYHA functional class III and IV patients, $P > .05$).

In summary, digoxin appeared to have no effect on QOL in patients with heart failure compared with placebo.

Discussion

Most heart failure trials attempting to measure HQOL, including the DIG trial, measure it by symptomatic relief using a restricted symptom questionnaire, measurements of general well-being, and a test of exercise tolerance. Unfortunately, only rare trials that have been completed in heart failure have shown clear improvement in HQOL,[7,25] with most showing modest,[4] equivocal,[26] or no significant improvement at all in quality of life, even if there is improvement in survival.[5,27,28] Even in studies that have used multiple self-report questionnaires and detailed interviews in addition to exercise function, significant improvement resulting from treatment has been difficult to establish.[29]

Withdrawal of digoxin has been shown to cause an increase in symptoms, a decline in exercise capacity, and an increased risk of hospitalization for worsening heart failure.[9,10] In this trial, however, the addition of digoxin to an otherwise stable medical regimen, which generally included an ACE inhibitor and a diuretic, did not show any effect of digoxin on QOL scores. The distance walked in the 6-minute walk test did increase in a statistically significant fashion but the actual increase in distance walked compared with the placebo group was trivial and not likely to be of clinical significance. We also noted small improvements in some of the HQOL measures in both the placebo and treatment groups at the 4- and 12-month intervals. Because the changes were all positive and seemed to occur in both the treatment and placebo arms of the study, this may simply reflect a general benefit of participating in the study, a phenomenon noted elsewhere.[30] Although the perceived health measure was significantly improved in the digoxin group compared with placebo at 4 months, the absence of any other improvements at that time suggests there was not really any overall short-term benefit of digoxin either; an early improvement in QOL measures has been noted with some other positive inotropes, although generally associated with subsequent worsening of survival.[31] Although the lack of improvement in HQOL scores was unexpected given the suggested decrease in hospitalization for heart failure in the DIG trial[8] and the symptomatic relief that has been reported with digoxin therapy,[9,10,32,33] this result is consistent with the several other major heart failure trials cited earlier.[4,5,27,28] There are several possible reasons for these results.

The lack of improvement in the digoxin treatment group could be attributed to a gradual adjustment of patients to the symptomatic effects of heart failure, which might subsequently make it more difficult to detect any benefits related to an intervention, given a smaller perceived benefit. The absolute values of HQOL data seen in this trial, which tend to run in the middle ranges of the measures variables despite the significant illness of the patients studied (see Table 4) support this interpretation. It has also been suggested that depression is common in patients with heart failure[2,3] and therefore it may be more difficult to achieve a significant change in QOL.

The lack of measured change in the HQOL parameters may reflect a lack of sensitivity to change of the scales themselves, as suggested in the Studies of Left Ventricular Dysfunction QOL analysis.[4] The size of the confidence intervals in Table 4 indicates a wide range of values for

each measure that did not shift despite treatment with digoxin, also suggesting a lack of sensitivity of the scales was employed. Thus, although the scales used could discriminate between NYHA function class I/II and class III/IV patients (see Table 3), they might not be able to detect smaller changes in HQOL that occur over the course of the study. Furthermore, some of the items measured (depression, anger, anxiety) may reflect relatively enduring long-term psychologic states and may not be subject to much change over time.[4] "Test-taking" behavior may also confound responses obtained with a questionnaire. Respondents tend to avoid selecting the extremes on a rating scale, and there may be a tendency to "carry over" responses from a previous questionnaire to a current version simply for the sake of convenience.[4]

It may also be that the effects of digoxin are too modest to produce a detectable improvement in HQOL when added to an already effective medical regimen. Indeed, it may be a combination of a lack of sensitivity of the HQOL assessment tools, along with the nature of digoxin's hemodynamic and neurohormonal effects, which led to the absence of effect on HQOL seen in this study. Digoxin has a relatively weak positive inotropic effect[34] and has only a modest direct effect on the autonomic nervous system itself, with neurohormonal changes seen in treated patients resulting from direct withdrawal of adrenergic activation[35] and sensitization of baroreceptors.[36] This small rise in contractility may be associated with an increase in measured ejection fraction along with other changes in hemodynamic variables in similar magnitude.[34] Although it is unclear as to which clinical or hemodynamic variables can predict exercise tolerance in patients with heart failure, ejection fraction does not predict exercise tolerance,[37] a result also confirmed in this study (see Table 4). Based on the effects of digoxin as a relatively weak inotrope with only modest neurohormonal effects, one would not predict a substantial effect on exercise tolerance, and by extrapolation, on HQOL.

As difficult as it might be to predict exercise tolerance, it is reassuring to note that in this study, a physician's assessment of a patient's functional class, which is by definition a subjective appraisal, did correlate well with a patient's self-perceived HQOL (see Table 3).

The patients in the HQOL substudy had a shorter duration of heart failure compared with the remaining patients in the DIG trial, although the baseline characteristics between the treatment and control groups for the substudy were similar; the very small difference in ejection fraction is probably of no clinical significance. The shorter duration of heart failure probably reflected ongoing recruitment to the trial and concurrent enrollment in the HQOL substudy by participating centers. Because enrollment in the substudy began partway through the 31 months of recruitment for the DIG trial, it is likely that patients who entered the trial first had preexisting heart failure and that the patients who were recruited later in the trial and who entered the substudy had developed heart failure as the trial was progressing, with, consequently, a shorter duration of their illness. Although one might therefore question whether the results of this substudy can be generalized to the remaining patient population with heart failure of longer duration, one could hypothesize that long-standing heart failure would be less likely to benefit from the effects of digoxin, with more adjustment to the syndrome, and perhaps a greater likelihood of developing depression.[3] The somewhat lower use of angiotensin-converting enzyme inhibitors and nitrates in the substudy is of uncertain significance, but should be considered as one attempts to generalize the findings of this report.

One additional question is whether the serum digoxin levels in the treated patients were sufficient to reach the full inotropic effect that may be achieved with the agent. There are few data in the literature to suggest a significant dose effect of digoxin on cardiac function.[38] In this study, it was not possible to address this issue because there were insufficient digoxin levels drawn to examine the possibility that an effect on HQOL was affected in either a positive or negative way by the serum digoxin level.

The efficacy of digoxin has been debated in the literature for years. Several well-designed clinical trials have indicated that when digoxin was withdrawn from a regimen including digoxin that had been adjusted to optimal control of the patient's heart failure, clinical deterioration often developed.[9,10] Indeed, one study demonstrated that the HQOL of patients withdrawn from digoxin deteriorated, using the Minnesota Living With Heart Failure questionnaire.[10] The difference in outcomes between these earlier trials and the present study probably lies in a fundamental difference in study design: patients in the earlier trials were optimized with a regimen including digoxin and then had digoxin withdrawn, whereas in the present study, less than half of the patients enrolled were already receiving digoxin, and the agent was then added to a regimen that had already been optimized. In other words, an assessment of digoxin's relative clinical effectiveness might be greater if it were removed from a drug regimen in a study in which diuretic (and possibly ACE inhibitor) doses were adjusted concurrently with digoxin administration, rather then as in the present study, where it was added to a drug regiment where diuretic and ACE inhibitor doses were already optimized. If, in the earlier trials, functional class deteriorated, one would expect a corresponding decline in HQOL, as would be predicted by the present study's results.

About one-third of the patients in this substudy had received digoxin within 1 week before randomization into the study, and one-half of these patients were

assigned to placebo. These patients were essentially withdrawn from their digoxin therapy. The duration of previous digoxin therapy was not recorded so it is unclear how many of these patients were receiving long-term digoxin therapy before their entry into this study. Nonetheless, it is reassuring to note there was no deterioration in the HQOL measures for these patients. There was actually an improvement in the Minnesota Living with Heart Failure measure in patients originally receiving digoxin randomized to placebo compared with those assigned to digoxin therapy, but the lack of improvement in any other measure suggests this finding is simply due to the play of chance; such an improvement does not make clinical sense.

Missing data can bias conclusions, especially if data are omitted because of a systematic process (i.e., if all responders who failed to complete questionnaires did so because they received placebo had died; therefore, no scores would have been reported). Sensitivity analysis attempts to evaluate the impact of the missing data by reevaluating the study conclusion as missing values are replaced with data based on various assumptions. In a study of this nature, the most reasonable analysis might be to impute the worst scores to avoid the possibility of concluding a benefit was derived from digoxin therapy when, in fact, none occurs (a type I error). This analysis, along with other analyses that assigned best scores to both groups and intermediate scores to both groups, failed to change the study conclusion of no digoxin effect. If best scores were imputed to either the digoxin or placebo group, and worst scores to the other group, however, all HQOL measures become significantly different between the two groups. Although these extreme responses are not totally impossible in real life, they are clinically implausible, with the imputation of intermediate values probably the most reasonable. Imputing worst values would be the safest choice with respect to avoiding a false-positive result. If there are enough missing data, the study results can clearly be affected by the assumptions used in the missing data analysis; this has been observed in other large trials of heart failure.[4]

In conclusion, in this subset of the DIG trial population, digoxin had no effect on measured QOL compared with placebo when added to a regimen consisting of diuretics and ACE inhibitors in patients with heart failure in sinus rhythm. Additional trials are needed in patients with heart failure to evaluate other drug regimens that may benefit HQOL and improve longevity.

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